Phenobarbitone versus phenytoin monotherapy for epilepsy: an individual participant data review

Review information

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Dates

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What's new

Date	Event	Description
21 August 2018	New citation: conclusions not changed	Conclusions are unchanged.
21 August 2018	Updated	Searches updated 21 August 2018, one new trial has been included. The term 'partial' has been replaced by 'focal', in accordance with the most recent classification of epilepsies of the International League Against Epilepsy (Scheffer 2017).

History

Date	Event	Description
30 July 2014	Updated	Searches updated.
31 May 2012	New citation: conclusions not changed	Searches updated 31 May 2012; no new trials identified. 'Risk of bias' and 'Summary of findings' tables added.
31 May 2012	Updated	Updated May 2012
11 November 2009	Updated	Searches updated 20 October 2009; no new trials identified.
22 December 2006	Updated	Searches updated 22 December 2006; no new trials identified.

Abstract

Background

This is an update of a Cochrane Review first published in 2001, and last updated in 2013. This review is one in a series of Cochrane Reviews investigating pair-wise monotherapy comparisons.

Epilepsy is a common neurological condition in which abnormal electrical discharges from the brain cause recurrent unprovoked seizures. It is believed that with effective drug treatment, up to 70% of individuals with active epilepsy have the potential to become seizure-free and go into long-term remission shortly after starting drug therapy with a single antiepileptic drug in monotherapy.

Worldwide, particularly in the developing world, phenytoin and phenobarbitone are commonly used antiepileptic drugs, primarily because they are inexpensive. The aim of this review is to summarise data from existing trials comparing phenytoin and phenobarbitone.

Objectives

To review the time to treatment failure, remission and first seizure with phenobarbitone compared with phenytoin when used as monotherapy in people with focal onset seizures (simple or complex focal and secondarily generalised), or generalised onset tonic-clonic seizures (with or without other generalised seizure types).

Search methods

For the latest update, we searched the following databases on 21 August 2018: the Cochrane Register of Studies (CRS Web), which includes Cochrane Epilepsy's Specialized Register and CENTRAL; MEDLINE; the US National Institutes of Health Ongoing Trials Register (ClinicalTrials.gov); and the World Health Organization International Clinical Trials Registry Platform (ICTRP). We handsearched relevant journals and contacted pharmaceutical companies, original trial investigators, and experts in the field.¬

Selection criteria

Randomised controlled trials comparing monotherapy with either phenobarbitone or phenytoin in children or adults with focal onset seizures or generalised onset tonic-clonic seizures.

Data collection and analysis

This was an individual participant data (IPD), review. Our primary outcome was time to treatment failure. Our secondary outcomes were time to first seizure post-randomisation, time to six-month remission and time to 12-month remission. We used Cox proportional hazards regression models to obtain trial-specific estimates of hazard ratios (HRs), with 95% confidence intervals (CIs), using the generic inverse variance method to obtain the overall pooled HR and 95% CI.

Main results

Individual participant data were obtained for five studies, which recruited a total of 635 participants, representing 80% of 798 individuals from all seven identified eligible trials. For remission outcomes, an HR of less than 1 indicates an advantage for phenytoin and for first seizure and treatment failure outcomes an HR of less than 1 indicates an advantage for phenobarbitone.

Results for the primary outcome of the review were: time to treatment failure for any reason related to treatment (pooled HR adjusted for seizure type for 499 participants: 1.61, 95% CI 1.22 to 2.12, low-certainty evidence), time to treatment failure due to adverse events (pooled HR adjusted for seizure type for 499 participants: 1.99, 95% CI 1.37 to 2.87, low-certainty evidence), time to treatment failure due to lack of efficacy (pooled HR adjusted

for seizure type for 499 participants: 1.87, 95% CI 1.32 to 2.66, moderate-certainty evidence), showing a statistically significant advantage for phenytoin compared to phenobarbitone.

For our secondary outcomes, we did not find any statistically significant differences between phenytoin and phenobarbitone: time to first seizure post-randomisation (pooled HR adjusted for seizure type for 624 participants: 0.85, 95% CI 0.69 to 1.06, moderate-certainty evidence), time to 12-month remission (pooled HR adjusted for seizure type for 588 participants: 0.90, 95% CI 0.69 to 1.19, moderate-certainty evidence), and time to six-month remission pooled HR adjusted for seizure type for 588 participants: 0.91, 95% CI 0.71 to 1.15, moderate-certainty evidence).

For individuals with focal onset seizures (73% of individuals contributing to analysis), numerical results were similar and conclusions the same as for analyses of all individuals and for individuals with generalised onset seizures (27% of individuals contributing to analysis), results were imprecise and no clear differences between the drugs were observed.

Several confounding factors, most notably the differences in design of the trials with respect to blinding, were likely to have impacted on the results of the primary outcome 'time to treatment failure', and in turn, the treatment failure rates may have impacted on the secondary efficacy outcomes of time to first seizure and time to 12-month and six-month remission.

Authors' conclusions

Low-certainty evidence from this review suggests that phenytoin may be a more effective drug than phenobarbitone in terms of treatment retention (treatment failures due to lack of efficacy or adverse events or both). Moderate-certainty evidence from this review also indicates no differences between the drugs in terms of time to seizure recurrence and seizure remission.

However, the trials contributing to the analyses had methodological inadequacies and methodological design differences that may have impacted upon the results of this review. Therefore, we do not suggest that results of this review alone should form the basis of a treatment choice for a patient with newly onset seizures. We recommend that future trials should be designed to the highest quality possible with consideration of masking, choice of population, classification of seizure type, duration of follow-up, choice of outcomes and analysis, and presentation of results.

Plain language summary

Phenobarbitone versus phenytoin monotherapy (single-drug treatment) for epilepsy

This is an updated version of the Cochrane Review previously published in 2013, Issue 1 of the *Cochrane Database of Systematic Reviews*.

Background

Epilepsy is a common neurological disorder in which abnormal electrical discharges from the brain cause recurrent seizures. We studied two types of epileptic seizures in this review: generalised onset seizures, in which electrical discharges begin in one part of the brain and move throughout the brain; and focal onset seizures, in which the seizure is generated in and affects one part of the brain (the whole hemisphere of the brain or part of a lobe of the brain). Focal seizures may become generalised (secondary generalisation), and move from one part of the brain throughout the brain. For around 70% of people with epilepsy, a single antiepileptic medication can control generalised onset or focal onset seizures.

This review applies to people with focal seizures (with or without secondary generalisation) and people with generalised tonic-clonic seizures, a specific generalised seizure type. This review does not apply to people with other generalised seizure types such as absence seizures or myoclonic seizures, as the recommended treatments for these seizure types are different.

Worldwide, particularly in low- and middle-income countries in Africa, Asia, and South America, phenobarbitone and phenytoin are commonly used antiepileptic drugs due to the low cost of these drugs.

Objective

The aim of this review was to compare how effective these drugs are at controlling seizures, to find out if they are associated with side effects that may result in individuals stopping the medication, and to inform a choice between these medications.

Methods

The last search for trials was in August 2018. We assessed the evidence from seven clinical trials in which people received either phenobarbitone or phenytoin and their treatment was decided randomly. We were able to combine data for 635 people from five of the seven trials; for the remaining 163 people from two trials, data were not available to use in this review

Key results

This review found no evidence to suggest a difference between phenobarbitone and phenytoin in terms of the time to seizure recurrence and time to seizure remission (seizure free period of six or 12 months). Phenobarbitone treatment was more likely to be withdrawn than phenytoin treatment, however, this may have

been influenced by the design of the included studies (whether the people and the clinicians treating them knew which treatment the person was receiving).

Quality of the evidence

Some of the trials contributing data to the review had methodological problems, which may have introduced bias and inconsistent results into this review. Also, we believe that the difference in study design with regards to whether the treatment was masked from the patients and clinicians (e.g. with a placebo tablet) had an impact on the rates of withdrawal from the study treatments, which also is likely to have impacted on the outcomes related to seizure control

These problems may have affected the results of this review and we judged the quality of the evidence provided by this review to be moderate to low quality. We do not suggest using the results of this review alone for making a choice between phenytoin or phenobarbitone for the treatment of epilepsy. Future trials comparing these drugs or any other antiepileptic drugs should be designed using high-quality methods to ensure results are also of high quality.

Background

This is an updated version of the Cochrane Review previously published in 2013, Issue 1 of the *Cochrane Database of Systematic Reviews* (Nolan 2013b).

Description of the condition

Epilepsy is a common neurological condition in which abnormal electrical discharges from the brain cause recurrent unprovoked seizures. Epilepsy is a disorder of many heterogenous seizure types, with an estimated incidence of 33 to 57 per 100,000 person-years worldwide (Annegers 1999; Hirtz 2007; MacDonald 2000; Olafsson 2005; Sander 1996), accounting for approximately 1% of the global burden of disease (Murray 1994).

The lifetime risk of epilepsy onset is estimated to be 1300 to 4000 per 100,000 person-years (Hauser 1993; Juul-Jenson 1983), and the lifetime prevalence could be as large as 70 million people worldwide (Ngugi 2010). It is believed that with effective drug treatment, up to 70% of individuals with active epilepsy have the potential to go into long-term remission shortly after starting drug therapy (Cockerell 1995; Hauser 1993; Sander 2004), and around 70% of individuals can achieve seizure freedom using a single antiepileptic drug in monotherapy (Cockerell 1995). Current National Institute for Health and Care Excellence (NICE), guidelines recommend that both adults and children with epilepsy should be treated with monotherapy, wherever possible (NICE 2012). The remaining 30% of individuals experience refractory or drug-resistant seizures, which often require treatment with combinations of antiepileptic drugs or alternative treatments, such as epilepsy surgery (Kwan 2000).

We studied two seizure types in this review: generalised onset seizures, in which electrical discharges begin in one part of the brain and move throughout the brain, and focal onset seizures, in which the seizure is generated in and affects one part of the brain (the whole hemisphere of the brain or part of a lobe of the brain).

Description of the intervention

Phenobarbitone and phenytoin are two of the earliest drugs licensed for the treatment of epileptic seizures and have been used as monotherapy for focal seizures and generalised tonic-clonic seizures for over 50 years (Gruber 1962).

Phenobarbitone and phenytoin are no longer considered as first-line agents in the USA and much of Europe due to worries over short- and long-term tolerability (Trimble 1988; Wallace 1997; Wilder 1995). One open-label paediatric trial in the UK (de Silva 1996), withdrew the phenobarbitone arm of the trial because of concerns about behavioural problems and difficulties getting paediatricians to randomise individuals. However, the largest reported randomised controlled trial (RCT), investigating phenobarbitone as monotherapy in adults with focal seizures (Mattson 1985), did not find phenobarbitone to be more associated with adverse events than other trial drugs (carbamazepine, phenytoin, and primidone). In fact, phenobarbitone was significantly associated with the lowest incidence of motor disturbances (ataxia (lack of voluntary coordination of muscle movements), incoordination, nystagmus, and tremor), and gastrointestinal problems.

However both drugs are still used as first-line drugs in low- and middle-income countries in Africa, Asia, and South America, primarily because they are inexpensive (Banu 2007; Ogunrin 2005; Pal 1998). A paediatric trial conducted in rural India (Pal 1998), comparing phenobarbitone with phenytoin, found no excess in behavioural side effects from phenobarbitone, but a trial in Nigerian adults (Ogunrin 2005), showed evidence of an association between phenobarbitone and worsening of cognitive impairments, particularly memory deficits.

Both phenobarbitone and phenytoin have been shown to have teratogenic (disturbances to foetal development), effects (Bromley 2014; Weston 2016), where the risk is estimated to be two to three times that of the general population (Meador 2008; Morrow 2006).

Phenobarbitone is associated with low folic acid levels and megaloblastic anaemia (anaemia characterised by many large immature and dysfunctional red blood cells; Meador 2008). In addition to concerns over

behavioural and cognitive adverse events, phenobarbitone is commonly associated with somnolence (sedation), and connective tissue abnormalities, such as Dupuytren's contracture and frozen shoulder (Baulac 2002), and exposure to phenobarbitone has also been shown to be associated with significantly higher rates of cardiac malformations compared to exposure to other antiepileptic drugs during pregnancy in a recent systematic review (Weston 2016).

Phenytoin is associated with long-term cosmetic changes including gum hyperplasia, acne and coarsening of the facial features (Mattson 1985; Scheinfeld 2003), as well as low folic acid levels, predisposing participants to megaloblastic anaemia (Carl 1992) and is associated with congenital abnormalities (Gladstone 1992; Morrow 2006; Meador 2008; Nulman 1997), particularly foetal hydantoin syndrome (Scheinfeld 2003). Furthermore, due to the pharmacokinetic profile of phenytoin, the plasma concentrations are difficult to predict and dosing will usually need to be informed by measuring plasma concentration.

How the intervention might work

Antiepileptic drugs suppress seizures by reducing neuronal excitability (MacDonald 1995). Phenobarbitone and carbamazepine are broad-spectrum treatments suitable for many seizure types, and both have an anticonvulsant mechanism through blocking ion channels, binding with neurotransmitter receptors, or through inhibiting the metabolism or reuptake of neurotransmitters (Ragsdale 1991; Willow 1985), and the modulation of gamma-aminobutyric acid-A (GABA-A), receptors (Granger 1995; Rho 1996).

Why it is important to do this review

The aim of this review was to summarise efficacy and tolerability data from existing trials comparing phenobarbitone and phenytoin when used as monotherapy treatments. Although individual trials have found no consistent differences in efficacy, the confidence intervals generated by these trials are wide, and they have not excluded important differences in efficacy, which synthesising the data of the individual trials may show.

There are difficulties in undertaking a systematic review of epilepsy monotherapy trials as the important efficacy outcomes require analysis of time-to-event data (for example, time to first seizure after randomisation). Although methods have been developed to synthesise time-to-event data using summary information (Parmar 1998; Williamson 2002), the appropriate statistics are not commonly reported in published epilepsy trials (Nolan 2013a; Williamson 2000). Furthermore, although most epilepsy monotherapy trials collect seizure data, there has been no uniformity in the definition and reporting of outcomes. For example, trials may report time to 12-month remission but not time to first seizure or vice versa, or some trials may define time to first seizure from the date of randomisation while others use the date of achieving maintenance dose. Trial investigators have also adopted differing approaches to the analysis, particularly with respect to the censoring of time-to-event data. For these reasons, we performed this review using individual participant data (IPD), which helps to overcome these problems. This review is one in a series of Cochrane IPD reviews investigating pair-wise monotherapy comparisons (Marson 2000; Nevitt 2017b; Nevitt 2018a; Nevitt 2018b; Nevitt 2018c; Nevitt 2018d; Nevitt 2019a). These data have also been included in IPD network meta-analyses of antiepileptic drug monotherapy (Nevitt 2017a; Tudur Smith 2007).

Objectives

To review the time to treatment failure, remission and first seizure with phenobarbitone compared with phenytoin when used as monotherapy in people with focal onset seizures (simple or complex focal and secondarily generalised), or generalised onset tonic-clonic seizures (with or without other generalised seizure types).

Methods

Criteria for considering studies for this review

Types of studies

- Randomised controlled trials (RCTs) using either an adequate method of allocation concealment (e.g. sealed opaque envelopes) or a quasi-randomised method of allocation (e.g. allocation by date of birth).
- Trials may have been double-blind, single-blind, or unblinded.
- Trials must be of parallel design; cross-over studies are not an appropriate design for measuring the long-term outcomes of interest in this review (see Types of outcome measures).
- Trials must include a comparison of phenobarbitone monotherapy with phenytoin monotherapy in individuals with epilepsy; therefore, cluster randomised studies are not an eligible design.

Types of participants

- We included children or adults with focal onset seizures (simple focal, complex focal or secondarily generalised tonic-clonic seizures), or generalised onset tonic-clonic seizures, with or without other generalised seizure types (in other words, those who had only generalised tonic-clonic seizures and those who had both generalised onset tonic-clonic seizures and generalised seizures of other types (e.g. absence,

myoclonic etc.)).
- We excluded individuals with other generalised seizure types alone without generalised tonic-clonic seizures (e.g. those who had only absence seizures without any generalised clonic tonic-seizures), due to differences in first-line treatment guidelines for other generalised seizure types (NICE 2012).
- We included individuals who had a new diagnosis of epilepsy or who had experienced a relapse following antiepileptic monotherapy withdrawal only, due to differences in first-line treatment guidelines for individuals with refractory epilepsy (NICE 2012).

Types of interventions

Phenobarbitone or phenytoin as monotherapy.

Types of outcome measures

Below is a list of outcomes we investigated in this review. Reporting of these outcomes in the original trial report was not an eligibility requirement for inclusion in this review.

Primary outcomes

Time to treatment failure (retention time). This was a combined outcome reflecting both efficacy and tolerability, as the following may have led to failure of treatment: continued seizures, side effects, non-compliance or the initiation of additional add-on treatment. This is an outcome to which the participant makes a contribution and is the primary outcome measure recommended by the Commission on Antiepileptic Drugs of the International League Against Epilepsy (ILAE 1998; ILAE 2006).

Time to treatment failure is considered according to three definitions.

- Time to treatment failure for any treatment-related reason (continued seizures, side effects, non-compliance or the initiation of additional add-on treatment)
- Time to treatment failure due to adverse events (i.e. side effects)
- Time to treatment failure due to lack of efficacy (i.e. continued seizures)

Secondary outcomes

- Time to first seizure post-randomisation
- Time to achieve 12-month remission (seizure-free period)
- Time to achieve six-month remission (seizure-free period)

Search methods for identification of studies

Electronic searches

The first searches for this review were run in 2001. Subsequent searches were run in December 2006, October 2009, May 2012, and July 2014. For the most recent update we searched the following databases on 21 August 2018. There were no language restrictions.

- The Cochrane Register of Studies (CRS Web), which includes the Cochrane Epilepsy Group Specialized Register and the Cochrane Central Register of Controlled Trials (CENTRAL), using the strategy outlined in Appendix 1.
- MEDLINE (Ovid, 1946 to August 20, 2018) using the strategy outlined in Appendix 2.
- ClinicalTrials.gov using the strategy outlined in Appendix 3.
- The World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) using the strategy outlined in Appendix 4.

Searching other resources

In addition, we handsearched relevant journals, and contacted pharmaceutical companies and researchers in the field to seek any ongoing or unpublished studies.

Data collection and analysis

Selection of studies

Two review authors (SJN and AGM) independently assessed trials for inclusion. Any disagreements were resolved my mutual discussion.

Data extraction and management

We requested the following IPD for all trials meeting our inclusion criteria.

Trial methods

- Method of generation of random list
- Method of concealment of randomisation
- Stratification factors
- Blinding methods

Participant covariates

- Gender
- Age

- Seizure types
- Time between first seizure and randomisation
- Number of seizures prior to randomisation (with dates)
- Presence of neurological signs
- Electroencephalographic (EEG), results
- Computerised tomography/magnetic resonance imaging (CT/MRI), results

Follow-up data

- Treatment allocation
- Date of randomisation
- Dates of follow-up
- Dates of seizures post-randomisation or seizure frequency data between follow-up visits
- Dates of treatment failure and reasons for treatment failure
- Dose
- Dates of dose changes

For each trial for which we did not obtain IPD, we carried out an assessment to see whether any relevant aggregate-level data have been reported or could be indirectly estimated using the methods of Parmar 1998 and Williamson 2002.

Two trials involving 414 participants, provided seizure data in terms of the number of seizures recorded between each follow-up visit rather than specific dates of seizures (Mattson 1985; Pal 1998). To enable the calculation of time-to-event outcomes, we applied linear interpolation to approximate dates of seizures between follow-up visits. For example, if the trial recorded four seizures between two visits that occurred on 1 March 1990 and 1 May 1990 (interval of 61 days), then the date of first seizure would be approximately 13 March 1990. This allowed the computation of an estimate of the time to six-month remission, 12-month remission, and first seizure.

We calculated time to six-month and 12-month remission from the date of randomisation to the date (or estimated date), that the individual had first been free of seizures for six or 12 months, respectively. If the person had one or more seizures in the titration period, a six-month or 12-month seizure-free period could also occur between the estimated date of the last seizure in the titration period and the estimated date of the first seizure in the maintenance period.

We calculated time to first seizure from the date of randomisation to the date that we estimated their first seizure to have occurred. If seizure data were missing for a particular visit, we censored these outcomes at the previous visit. We also censored these outcomes if the individual died or if follow-up ceased prior to the occurrence of the event of interest. We used these methods in the remaining three trials involving 221 participants (de Silva 1996; Heller 1995; Ogunrin 2005), for which we directly received outcome data (dates of seizures after randomisation).

In the Ogunrin 2005 trial, all 36 participants completed the 12-week trial duration and no participants withdrew from the trial or from the allocated treatment and no treatment failure data were available for Pal 1998. For the remaining three trials (505 participants), we extracted dates and reason for treatment failure or withdrawal from trial case report forms for the original review (de Silva 1996; Heller 1995; Mattson 1985).

Two review authors (SJN and AGM) independently extracted data from all case report forms, resolving disagreements by reconsidering the case report forms at conference. For the analysis of time-to-event data, we defined an 'event' as either the failure of the allocated treatment because of poor seizure control, adverse events, or both. We also classed non-compliance with the treatment regimen or the addition of another antiepileptic drug as 'events' for the outcome 'time to treatment failure.' We censored the outcome if treatment was stopped because the individual achieved a period of remission or if the individual was still on allocated treatment at the end of follow-up.

Assessment of risk of bias in included studies

Two review authors (SJN and CTS), independently assessed all included trials for risk of bias according to the Cochrane 'Risk of bias' tool (Higgins 2017), resolving any disagreements by discussion. We rated each of the following six domains as low, unclear or high risk of bias: method of generating random sequence, allocation concealment, blinding methods, incomplete outcome data, selective outcome reporting and other sources of bias. Any discrepancies in the two authors' 'Risk of bias' judgements were resolved by discussion.

Measures of treatment effect

We measured all outcomes in this review as time-to-event outcomes with the hazard ratio (HR), and 95% confidence interval (CI), used as the measure of treatment effect. We calculated outcomes from IPD provided, where possible, or extracted from published trials if possible.

Unit of analysis issues

We did not have any unit of analysis issues. The unit of allocation and analysis was individual for all included trials, and no trials included in meta-analysis were of a repeated measures (longitudinal), nature or of a cross-over design.

Dealing with missing data

For each trial that supplied IPD, we reproduced results from trial results where possible and performed consistency checks.

- We cross-checked trial details against any published report of the trial and contacted original trial authors if we found missing data, errors, or inconsistencies.
- If trial authors could not resolve inconsistencies between IPD and published data, depending on the extent of the inconsistencies, we performed sensitivity analysis (see Sensitivity analysis), or excluded the data from the meta-analysis.
- We reviewed the chronological randomisation sequence and checked the balance of prognostic factors, taking account of factors stratified for in the randomisation procedure.

Assessment of heterogeneity

We assessed heterogeneity statistically using the Q test ($P < 0.10$ for significance), and the I^2 statistic (greater than 50% indicating considerable heterogeneity; Higgins 2003), output produced using the generic inverse variance approach in Data and analyses, and visually by inspecting forest plots.

Assessment of reporting biases

Two review authors (SJN and CTS), undertook all full quality and 'Risk of bias' assessments. In theory, a review using IPD should overcome issues of reporting biases, as unpublished data can be provided and unpublished outcomes calculated. Any selective reporting bias detected could be assessed with the Outcome Reporting Bias In Trials (ORBIT), classification system (Kirkham 2010).

Data synthesis

We carried out our analysis on an intention-to-treat basis (that is, we analysed participants in the group to which they were randomised, irrespective of which treatment they actually received). Therefore, for the time-to-event outcomes 'time to six-month remission', 'time to 12-month remission', and 'time to first seizure post-randomisation', we did not censor participants if treatment was withdrawn or failed.

For all outcomes, we investigated the relationship between the time-to-event and treatment effect of the antiepileptic drugs. We used Cox proportional hazards regression models to obtain trial-specific estimates of log (HR), or treatment effect and associated standard errors in Stata Statistical Software, version 14 (Stata 2015). The model assumes that the ratio of hazards (risks), between the two treatment groups is constant over time (i.e. hazards are proportional). We tested this proportional hazards assumption of the Cox regression model for each outcome of each trial by testing the statistical significance of a time-varying covariate in the model. We evaluated overall estimates of HRs (with 95% confidence intervals (CIs)), using the generic inverse variance method. We expressed results as anHR and a 95% CI.

By convention, an HR greater than 1 indicates that an event is more likely to occur earlier on phenobarbitone than on phenytoin. Hence, for time to treatment failure or time to first seizure, an HR greater than 1 indicates a clinical advantage for phenytoin (e.g. an HR of 1.2 would suggest a 20% increase in risk of treatment failure from phenobarbitone compared to phenytoin), and for time to six-month and 12-month remission, an HR greater than 1 indicates a clinical advantage for phenytoin.

Subgroup analysis and investigation of heterogeneity

To examine the potential impact of seizure type on results, we stratified all analyses by seizure type (focal onset versus generalised onset), according to the classification of main seizure type at baseline. We classified focal seizures (simple or complex), and focal secondarily generalised seizures as focal epilepsy.

We classified primarily generalised seizures as generalised epilepsy. We conducted a Chi^2 test of interaction between treatment and seizure type. If we found significant statistical heterogeneity to be present, we performed meta-analysis with a random-effects model in addition to a fixed-effect model, presenting the results of both models and performing sensitivity analyses to investigate differences in trial characteristics.

Sensitivity analysis

We performed several sensitivity analyses to test the robustness of our results to characteristics of the included trials.

- de Silva 1996 withdrew the phenobarbitone arm of the trial after 10 children were randomised to phenobarbitone due to concerns over unacceptable side effects. The trial did not randomise any further children to phenobarbitone and continued with the three other treatment arms: carbamazepine, phenytoin, and sodium valproate. For the primary and secondary outcomes of this review, we included all children randomised to phenytoin (n = 54), and phenobarbitone (n = 10), from de Silva 1996, and to account for the imbalance between children randomised to the two drugs on this trial, we performed sensitivity analysis including only those children who were randomised before the withdrawal of the phenobarbitone arm from the trial. For sensitivity analysis, we analysed 19 children (11 boys and eight girls), 10 randomised to phenobarbitone and nine randomised to phenytoin, 11 with generalised seizures and eight with focal seizures. We performed this sensitivity analysis for each outcome and observed any change to results and conclusions.
- Misclassification of seizure type is a recognised problem in epilepsy, whereby some people with

generalised seizures have been mistakenly classed as having focal onset seizures and vice versa. There is clinical evidence that individuals with generalised onset seizures are unlikely to have an 'age of onset' greater than 25 to 30 years (Malafosse 1994). Such misclassification affected the results of three reviews in our series of pair-wise reviews for monotherapy in epilepsy comparing carbamazepine to phenobarbitone, phenytoin and sodium valproate in which around 30% to 50% of participants analysed may have had their seizure type misclassified as generalised onset (Marson 2000; Nevitt 2017b; Nevitt 2018b). Given the potential biases introduced into those reviews, we examined the distribution of age at onset for individuals with generalised seizures in the trials included in this review, to assess the potential impact of misclassification of seizure type on the outcomes.
  - 33 out of 68 individuals (49%), with generalised onset seizures were over the age of 30 in Heller 1995,
  - 13 out of 31 individuals (42%), with generalised onset seizures were over the age of 30 in Ogunrin 2005

de Silva 1996 and Pal 1998 were paediatric trials, and Mattson 1985 recruited participants with focal seizures only, so there were no participants with new onset generalised seizures over the age of 30 in these trials. Therefore, out of 162 participants classified as experiencing generalised seizures from the five trials providing IPD, 46 (28%), may have been wrongly classified.

To investigate misclassification for each outcome, we undertook the following two analyses to investigate misclassification.

- We reclassified all individuals with generalised seizures and age at onset greater than 30 into an 'uncertain seizure type' group.
- We reclassified individuals with generalised seizures and age at onset greater than 30 as having focal onset seizures.

'Summary of findings' tables and certainty of the evidence (GRADE)

For this 2019 update, we added two 'Summary of findings' tables to the review (outcomes in the tables decided before the update started based on clinical relevance).

Summary of findings table 1 reports the primary outcome of 'time to treatment failure' in the subgroups of participants with focal onset seizures, generalised onset seizures and overall adjusted by seizure type.

Summary of findings table 2 reports the secondary outcomes of 'time to first seizure' and 'time to 12-month remission' in the subgroups of participants with focal onset seizures, generalised onset seizures and overall adjusted by seizure type.

We determined the quality of the evidence using the GRADE approach, where we downgraded evidence in the presence of high risk of bias in at least one trial, indirectness of the evidence, unexplained heterogeneity or inconsistency, imprecision of results and high probability of publication bias. We downgraded evidence by one level if we considered the limitation serious and two levels for very serious.

Results

Description of studies

Results of the search

In previous versions of the review (Nolan 2013b, Taylor 2001), eight studies were included (Cereghino 1974; Czapinski 1997; de Silva 1996; Gruber 1962; Heller 1995; Mattson 1985; Pal 1998; Thilothammal 1996) and five studies were listed as excluded (Bird 1966; Cereghino 1975; Meador 1990; Verma 2010; White 1966). In this update of the review, we have updated the inclusion and exclusion criteria of the review and cross-over design studies have been excluded as this design is not appropriate for measuring the long-term outcomes of the review. Therefore two previously included cross-over studies now excluded from the review (Cereghino 1974; Gruber 1962).

For this update, from electronic searches conducted in July 2014 and August 2018, we identified 75 records from the databases and search strategies outlined in Electronic searches. We found one further record by searching other resources (an included study within another Cochrane Review (Nevitt 2017a)). We removed six duplicate records and screened 69 records (title and abstract), for inclusion in the review. We excluded 69 records based on the title and abstract and assessed one full-text articles for inclusion in the review. We excluded seven trials (see Excluded studies below), and included seven trials in the review (see Included studies). See Figure 1 for a PRISMA study flow diagram (Moher 2009).

Included studies

Seven studies were identified as eligible for this systematic review (Czapinski 1997; de Silva 1996; Heller 1995; Mattson 1985; Ogunrin 2005; Pal 1998; Thilothammal 1996)

Four of the studies recruited adults (Czapinski 1997; Heller 1995; Mattson 1985; Ogunrin 2005) and three recruited children (de Silva 1996; Pal 1998; Thilothammal 1996). Four studies recruited individuals with focal onset and generalised onset seizures (de Silva 1996; Heller 1995; Pal 1998; Ogunrin 2005), two recruited individuals with focal onset seizures only (Czapinski 1997; Mattson 1985), one recruited individuals with generalised onset seizures only (Thilothammal 1996). Six trials recruited individuals with new onset seizures, or previously untreated seizures, or both (Czapinski 1997; de Silva 1996; Heller 1995;

Ogunrin 2005; Pal 1998; Thilothammal 1996) one trial recruited "previously untreated or under-treated" individuals (Mattson 1985)

Three studies were conducted in Europe (Czapinski 1997; de Silva 1996; Heller 1995), two studies were conducted in India (Pal 1998; Thilothammal 1996), one study was conducted in the USA (Mattson 1985), and one study was conducted in Nigeria (Ogunrin 2005).

Individual participant data (IPD) were obtained for five studies, which recruited a total of 635 participants, representing 80% of 798 individuals from all seven identified eligible trials. For three trials, computerised data were directly provided (Mattson 1985; Ogunrin 2005; Pal 1998), and the authors of two trials (de Silva 1996; Heller 1995) supplied a combination of both computerised and hard copy data (although mostly computerised).

Data were available for the following participant characteristics (percentage of 635 participants with data available): epilepsy type (100%), age at randomisation (99%, data missing for two participants from Mattson 1985), sex (99%, data missing for two participants from Mattson 1985 and two participants from Pal 1998); drug randomised (99%, data missing for six participants in de Silva 1996), time since first seizure to randomisation (94%, data missing for all 36 participants from Ogunrin 2005, two participants from Mattson 1985, two participants from Pal 1998, and one participant from Heller 1995); number of seizures in six months prior to randomisation (85%, data missing for all 94 participants from Pal 1998 and for three participants from Mattson 1985). See the Characteristics of included studies and Table 1 for further details.

Four trials provided the results of neurological examinations for 315 participants (50% of total participants with IPD provided; de Silva 1996; Heller 1995; Ogunrin 2005; Pal 1998). All participants had a normal neurological examination in Ogunrin 2005, 91% of participants in both de Silva 1996 and Heller 1995 had a normal neurological examination. However, in Pal 1998, 74% of participants were reported to have an abnormal neurological examination.

Electroencephalographic (EEG) and computerised tomography (CT) data were provided for 307 and 273 participants respectively from Mattson 1985; 71% of participants with EEG data had an abnormal EEG and 27% of participant with CT data had an abnormal scan. Ogunrin 2005 reported that none of the 36 participants had an abnormal scan. EEG and CT data were not available for the other three studies (de Silva 1996; Heller 1995; Pal 1998).

The largest study (Mattson 1985) contributing 320 participants (50% of total IPD provided) recruited participants with focal onset seizures only, therefore, of the 635 participants analysed, only 167 (26%) had generalised onset seizures.

We did not obtain IPD for the remaining two studies, with a total of 163 participants (20% of total eligible data), as we were not able to make contact with original trial authors to request data (Thilothammal 1996), or authors did not provide IPD, despite responding positively to our requests (Czapinski 1997). Neither of these trials reported the specific time-to-event outcomes chosen for this review, and we could not extract sufficient aggregate data from the trial publications in any other trial. Therefore, we could not include them in data synthesis. Table 2 contains full details of outcomes considered and summaries of results in each eligible trial for which IPD were not available.

Excluded studies

We excluded seven studies from this review. Two studies made polytherapy comparisons (Cereghino 1975; White 1966), or it was unclear if a monotherapy comparison was made in the study (Bird 1966; Meador 1990). Two studies were cross-over studies (Cereghino 1974; Gruber 1962), a design which is not appropriate for measuring the long-term outcomes in this review and one study recruited participants with neonatal seizures due to birth asphyxia, rather than epileptic seizures (Verma 2010). See Characteristics of excluded studies tables for further details.

Risk of bias in included studies

For further details see Characteristics of included studies, Figure 2 and Figure 3

Allocation (selection bias)

Trials for which we received IPD

Two of the trials randomised participants via a random list generated from random permuted blocks and used sealed opaque envelopes as the method of concealment of randomisation; these trials were judged to be at low risk of selection bias (de Silva 1996; Heller 1995). One trial used simple randomisation from a random number table with allocation of treatments taking place at a different site and was also judged to be at low risk of selection bias (Ogunrin 2005).

One trial randomised participants with a prepared random number list and by minimisation (low risk of bias) but did not provide any information regarding allocation concealment (unclear risk of bias) (Pal 1998). The final trial did not state the method of randomisation or allocation concealment used and was judged to be at unclear risk of selection bias (Mattson 1985).

Trials for which no IPD were available

One trial randomised participants using computer-generated random numbers and was judged to

be at low risk of bias (Thilothammal 1996), while Czapinski 1997 was judged to be at unclear risk of bias as the trial was described as 'randomised' but no details of the randomisation method were provided. The method of allocation concealment was not stated either of the studies so both studies were judged to be at unclear risk of bias.

Blinding (performance bias and detection bias)

Trials for which we received IPD

Two trials were completely unblinded for quote: "practical and ethical reasons" and were judged to be at high risk of performance bias and detection bias (de Silva 1996; Heller 1995). One trial did not blind participants and personnel for quote: "practical and ethical reasons" but single blinded for outcome (Pal 1998); we judged this trial to be at high risk of performance bias but low risk of detection bias.

One trial was double-blinded (participants and personnel), achieved using an additional placebo tablet (Mattson 1985) and one trial blinded participants (placebo tablet) and outcome assessors (Ogunrin 2005); both trials were judged to be at low risk of performance bias and detection bias.

Trials for which no IPD were available

One trial was double-blinded (participants and personnel), achieved using additional blank tablets and was judged to be at low risk of bias (Thilothammal 1996). Blinding was not mentioned in Czapinski 1997 so we judged this study to be at unclear risk of bias.

Incomplete outcome data (attrition bias)

Trials for which we received IPD

In theory, a review using IPD should overcome issues of attrition bias as unpublished data can be provided, unpublished outcomes calculated, and all randomised participants can be analysed by an intention-to-treat approach. All five trials provided IPD for all randomised individuals and reported the extent of follow-up for each individual; we judged all five trials to be at low risk of attrition bias (de Silva 1996; Heller 1995; Mattson 1985; Ogunrin 2005; Pal 1998). We queried any missing data with the original trial authors. From the information provided by the trial authors, we deemed the small amount of missing data present (see Included studies), to be missing at random and not affecting our analysis.

Trials for which no IPD were available

One trial reported attrition rates and analysed all randomised participants using an intention-to-treat approach so was judged to be at low risk of bias (Thilothammal 1996). The other trial reported attrition rates, but it was unclear if all participants were analysed (by an intention-to-treat approach or otherwise), therefore this trial was judged to be at unclear risk of attrition bias (Czapinski 1997).

Selective reporting (reporting bias)

We requested trial protocols in all IPD requests; however, protocols were not available for any of the seven trials included in the review, so we made a judgement of the risk of bias based on the information included in the publications or from the IPD we received (see the 'Characteristics of included studies' tables for more information).

Trials for which we received IPD

Trials for which we received IPD In theory, a review using IPD should overcome issues of reporting biases as unpublished data can be provided and unpublished outcomes calculated so all trials providing IPD were judged to be at low risk of reporting bias. We received sufficient IPD to calculate the four outcomes ('time to treatment failure', 'time to six-month remission, 'time to 12-month remission', and 'time to first seizure'), for three of the six trials (de Silva 1996; Heller 1995; Mattson 1985). The trial duration of Ogunrin 2005 was 12 weeks, and all randomised participants completed the trial; therefore, we could only calculate 'time to first seizure' for this trial. Treatment failure data were not available for Pal 1998.

Trials for which no IPD were available

One trial reported seizure reduction and adverse event outcomes well and therefore was judged to be at low risk of reporting bias (Thilothammal 1996). The other trial was available in abstract form only (Czapinski 1997) and did not provide sufficient information to assess selective reporting bias (unclear risk of reporting bias).

Other potential sources of bias

No other sources of bias were identified in six of the seven studies (de Silva 1996; Heller 1995; Mattson 1985; Ogunrin 2005; Pal 1998; Thilothammal 1996). One trial which was available in abstract form only (Czapinski 1997) reported very limited methodological information therefore it is unclear if there were any other potential sources of bias.

Effects of interventions

We have provided a summary of the outcomes reported in trials for which no IPD were available in Table 2.

See Table 3 for details regarding the number of individuals contributing IPD to each analysis, Summary of

findings table 1 for a summary of the results for the primary outcome 'time to treatment failure' (stratified by seizure type), and Summary of findings table 2 for a summary of results for the secondary outcomes 'time to first seizure' and 'time to 12-month remission'.

Survival curve plots are shown in Figure 4; Figure 5; Figure 6; Figure 7; Figure 8; Figure 9; Figure 10; Figure 11; Figure 12; Figure 13; Figure 14 and Figure 15 .

We used Stata software version 14 to produce all survival curve plots using data from all trials providing IPD combined (Stata 2015). We note that participants with event times of zero (i.e. those who experienced treatment failure or experienced seizure recurrence on the day of randomisation), are not included in the 'Numbers at risk' on the graphs and that data are not stratified by trial within these survival curve plots. All figures are intended to provide a visual representation of outcomes, extent of follow-up and visual differences between seizure types. These graphs are not intended to show statistical significance and numerical values may vary compared to the text due to differences in methodology.

We calculated all hazard ratios (HRs), presented below by fixed-effect generic inverse variance meta-analysis unless otherwise stated. All analyses met the assumption of proportional hazards (addition of time-varying covariate into the model non-significant), unless otherwise stated.

Primary outcome

Time to treatment failure (retention time)

For this outcome, an HR of less than one indicates a clinical advantage for phenobarbitone.

Times to treatment failure and reasons for treatment failure were available for 499 participants from three of the five trials providing IPD (78.6% of 635 participants from de Silva 1996, Heller 1995 and Mattson 1985 and 62.4% of the total 798 participants from the seven included trials). See Table 4 for reasons for premature discontinuation of treatment (treatment failure), by treatment and how we classified these reasons in analysis.

de Silva 1996 did not record the randomised drug for six participants, and the reason for treatment failure was not available for one participant randomised to phenytoin and could not be determined from the case notes. Similarly, in Heller 1995, for three participants randomised to phenobarbitone, the reason for treatment failure was not available and could not be determined from the case notes. For another two participants randomised to phenytoin in Heller 1995, the reason for treatment failure was available, but the treatment failure time was not available for these participants. All participants completed the 12-week trial in Ogunrin 2005 and treatment failure data were not available for Pal 1998, so these two trials could not contribute to the analysis of 'time to treatment failure.' Therefore, 499 participants contributed to the analysis of 'time to treatment failure' and reasons for 501 participants are presented in Table 4.

Out of the 501 participants for whom we had reasons for treatment failure or withdrawal (de Silva 1996, Heller 1995; Mattson 1985), 330 participants prematurely withdrew from treatment (66% of total participants): 156 out of 220 participants randomised to phenobarbitone (71%), and 174 out of 281 participants randomised to phenytoin (62%).

We deemed 212 participants (64% of total treatment failures), to have withdrawn for reasons related to the trial drug, 111 (71% of total treatment failures), on phenobarbitone and 101 (58% of total treatment failures), on phenytoin, and we classed these reasons as 'events' in analysis.

The most common treatment-related reason for treatment failure was a combination of adverse events and lack of efficacy: 93 withdrawals (44% of total treatment failures); 53 (48% of total treatment failures) on phenobarbitone and 40 (40% of total treatment failures) on phenytoin. Non-compliance with treatment or patient choice was the treatment-related reason in 21% of total treatment failures, lack of efficacy in 21% of total treatment failures and adverse events in 14% of total treatment failures.

We classed the other 94 reasons (32 on phenobarbitone and 62 on phenytoin), which were mostly losses to follow-up (48% of other withdrawals) or participants going into remission (45% of other withdrawals), to be not related to the treatment and censored these participants in the analysis, in addition to the 171 participants (64 on phenobarbitone and 107 on phenytoin), who completed the trial without withdrawing or failing treatment.

Considering time to treatment failure for any reason related to the treatment, the overall pooled HR (for 499 participants in three trials) was 1.61 (95% CI 1.22 to 2.12; P = 0.0007, low-certainty evidence; Analysis 1.1), indicating that treatment failure occurs significantly earlier on phenobarbitone compared to phenytoin. However, a substantial amount of statistical heterogeneity was present between trials (I^2 = 71%). When analysis is repeated with random-effects, the pooled HR was 2.10 (95% CI 1.09 to 4.05, P = 0.03), indicating that when variation between trials is accounted for, phenobarbitone was still significantly more likely to be withdrawn earlier than phenytoin but the confidence intervals of the pooled effect are wide, therefore we are unsure of the magnitude of the advantage to phenytoin. This heterogeneity is investigated further in subgroup analyses (see below).

Considering time to treatment failure due to adverse events (all other reasons for treatment failure or treatment withdrawal censored in analysis), the overall pooled HR (for 499 participants in three trials), was 2.01 (95% CI 1.39 to 2.90; P = 0.0002; low-certainty evidence; Analysis 1.2), indicating that treatment failure due to adverse

events occurs significantly earlier on phenobarbitone compared to phenytoin. However, a substantial amount of statistical heterogeneity was present between trials (I^2 = 78%). When analysis is repeated with random-effects, the pooled HR was 3.49 (95% CI 1.15 to 10.66, P = 0.03), indicating that when variation between trials is accounted for, phenobarbitone was still significantly more likely to be failed earlier than phenytoin but the confidence intervals of the pooled effect are wide, therefore we are unsure of the magnitude of the advantage to phenytoin. From visual inspection of the forest plot of Analysis 1.2, the HRs of one trial was around 1.5 (Mattson 1985) while the HRs of the other two trials were much larger (HR around 6 to 6.6 respectively) and confidence intervals of the HRs were very wide (de Silva 1996, Heller 1995). Table 4 shows an imbalance between the drugs between the number of participants failing treatment due to adverse events in de Silva 1996 and Heller 1995; very few participants on phenytoin failed treatment due to adverse events compared to participants on phenobarbitone in these trials. This explains the extreme and imprecise HRs for these two trials and may explain the moderate amount of heterogeneity between trials. The heterogeneity is also investigated further in subgroup analyses (see below).

Considering time to treatment failure due to lack of efficacy (all other reasons for treatment failure or treatment withdrawal censored in analysis), the overall pooled HR (for 499 participants in three trials) was 1.85 (95% CI 1.31 to 2.62; P = 0.0005, moderate-certainty evidence; Analysis 1.3), indicating that treatment failure due to lack of efficacy occurs significantly earlier on phenobarbitone compared to phenytoin. No important heterogeneity was present between trials (I^2 = 15%).

Subgroup analyses: seizure type (focal versus generalised onset)

Considering time to treatment failure for any reason related to the treatment, for individuals with focal onset seizures (404 participants from three trials), the pooled HR was 1.46 (95% CI 1.09 to 1.96, P = 0.01, I^2 = 53%, low-certainty evidence), indicating that treatment failure occurs significantly earlier on phenobarbitone compared to phenytoin. For individuals with generalised onset seizures (95 participants from two trials), the pooled HR was 4.04 (95% CI 1.61 to 10.14, P = 0.003, I^2 = 0%; low-certainty evidence), indicating that treatment failure occurs significantly earlier on phenobarbitone compared to phenytoin. There is statistically significant evidence of an interaction between epilepsy type (focal onset versus generalised onset) and treatment effect (test of subgroup differences: P = 0.04, I^2 = 76.5%; Analysis 1.4), in other words, it appears that the treatment effect of phenytoin over phenobarbitone may be larger for individuals with generalised onset seizures compared to individuals with focal onset seizures.

The overall pooled HR (adjusted by epilepsy type for 499 participants from three trials) was 1.61 (95% CI 1.22 to 2.12, P = 0.0008, low-certainty evidence; Analysis 1.4), indicating that treatment failure occurs significantly earlier on phenobarbitone compared to phenytoin.

A substantial amount of statistical heterogeneity was present between trials (I^2 = 53%) overall and for individuals with focal onset seizures. When analysis is repeated with random-effects, the pooled HR for all individuals was 2.32 (95% CI 1.28 to 4.20, P = 0.005) and for individuals with focal onset seizures was 1.83 (95% CI 0.97 to 3.47, P = 0.06), indicating that when variation between trials is accounted for, the advantage to phenobarbitone is still statistically significant for all individuals, but no longer statistically significant for individuals with focal onset seizures. The confidence intervals of the pooled effect are wide for these random-effect analyses, in addition to the confidence intervals of the pooled effect for individuals with generalised onset seizures (likely due to the small number of participants with generalised onset seizures failing treatment due to adverse events in these trials, see Table 4). Therefore we are unsure of the magnitude of the advantage to phenytoin overall and for both seizure types. In random-effects analysis, there is no longer statistically significant evidence of an interaction between epilepsy type (focal onset versus generalised onset) and treatment effect (test of subgroup differences: P = 0.17, I^2 = 47.7).

Considering time to treatment failure due to adverse events, for individuals with focal onset seizures (404 participants from three trials), the pooled HR was 1.86 (95% CI 1.27 to 2.73, P = 0.001, I^2 = 73%, low-certainty evidence), indicating that treatment failure due to adverse events occurs significantly earlier on phenobarbitone compared to phenytoin. For individuals with generalised onset seizures (95 participants from two trials), the pooled HR was 4.60 (95% CI 1.17 to 17.98, P = 0.03, I^2 = 0%; low-certainty evidence), indicating that treatment failure due to adverse events occurs significantly earlier on phenobarbitone compared to phenytoin. There was no evidence of an interaction between epilepsy type (focal onset versus generalised onset) and treatment effect (test of subgroup differences: P = 0.21, I^2 = 36.2%; Analysis 1.5).

A substantial amount of statistical heterogeneity was present between trials (I^2 = 73%) for individuals with focal onset seizures. When analysis is repeated with random-effects, the pooled HR was 3.52 (95% CI 1.04 to 11.95, P = 0.04), indicating that when variation between trials is accounted for, phenobarbitone was still significantly more likely to be failed earlier than phenytoin but the confidence intervals of the pooled effect are wide. The confidence intervals of the pooled effect are also wide for individuals with generalised onset seizures (likely due to the small number of participants with generalised onset seizures failing treatment due to adverse events in these trials, see Table 4). Therefore we are unsure of the magnitude of the advantage to phenytoin for both seizure types.

The overall pooled HR (adjusted by epilepsy type for 499 participants from three trials) was 1.99 (95% CI 1.37 to 2.87, P = 0.0003, low-certainty evidence; Analysis 1.5), indicating that treatment failure due to adverse events

occurs significantly earlier on phenobarbitone compared to phenytoin. However, a substantial amount of statistical heterogeneity was present between trials (I^2 = 58%). When analysis is repeated with random-effects, the pooled HR was 3.66 (95% CI 1.49 to 8.96, P = 0.005), indicating that when variation between trials is accounted for, phenobarbitone was still significantly more likely to be failed earlier than phenytoin but the confidence intervals of the pooled effect are wide, therefore we are unsure of the magnitude of the advantage to phenytoin.

Considering time to treatment failure due to lack of efficacy, for individuals with focal onset seizures (404 participants from three trials), the pooled HR was 1.73 (95% CI 1.19 to 2.52, P = 0.004, I^2 = 0%; moderate-quality evidence) and for individuals with generalised onset seizures (95 participants from two trials), the pooled HR was 3.40 (95% CI 1.21 to 9.54, P = 0.02, I^2 = 0%; low-certainty evidence). Both results indicate that treatment failure due to lack of efficacy occurs significantly earlier on phenobarbitone compared to phenytoin, but for individuals with generalised onset seizures, the confidence intervals of the pooled effect are wide, therefore we are unsure of the magnitude of the advantage to phenytoin. There was no evidence of an interaction between epilepsy type (focal onset versus generalised onset) and treatment effect (test of subgroup differences: P = 0.23, I^2 = 31.1%; Analysis 1.6).

The overall pooled HR (adjusted by epilepsy type for 499 participants from three trials) was 1.87 (95% CI 1.32 to 2.66, P = 0.0005, I^2 = 0%; moderate-certainty evidence; Analysis 1.6), indicating that treatment failure due to lack of efficacy occurs significantly earlier on phenobarbitone compared to phenytoin.

Additional subgroup analyses to investigate heterogeneity

A large amount of heterogeneity (I^2 > 70%) was present in the analyses of 'Time to treatment failure (any reason related to treatment)' and 'Time to treatment failure due to adverse events' for all participants (see Analysis 1.1, Analysis 1.2). This heterogeneity does not seem to be completely explained by differences in seizure type (focal versus generalised onset) as a large amount of heterogeneity (I^2 > 50%) is still present for these outcomes for individuals with focal onset seizures (see Analysis 1.4, Analysis 1.5). We considered two further possible sources of heterogeneity, age of the participants recruited and presence of blinding in the study.

- We performed a subgroup analysis combining two studies of adults (Heller 1995; Mattson 1985) compared with a study of children only (de Silva 1996).
  - Considering time to treatment failure for any reason related to the treatment, for 436 adults, the pooled HR is 1.46 (95% CI 1.09 to 1.95, P = 0.01, I^2=57%) and for the 63 children, the HR is 3.93 (95% CI 1.65 to 9.34, P = 0.002). There is statistically significant evidence of an interaction between age of the participants (adults versus children) and treatment effect (test of subgroup differences: P = 0.03, I^2 = 78.0%, Analysis 1.7).
  - Considering time to treatment failure due to adverse events, for 436 adults, the pooled HR is 1.75 (95% CI 1.18 to 2.58, P = 0.005, I^2 = 80%) and for the 63 children, the HR is 5.99 (95% CI 1.99 to 17.96, P = 0.001). There is statistically significant evidence of an interaction between age of the participants (adults versus children) and treatment effect (test of subgroup differences: P = 0.04, I^2 = 76.6%, Analysis 1.8).
  - In other words, for both adults and children, a significant advantage is observed for phenytoin (i.e. treatment failure for any reason or due to adverse events occurs later on phenytoin than phenobarbitone) and this advantage to phenytoin seems to be significantly larger for children compared to adults.
  - However, the heterogeneity present within the analyses of these outcomes still does not seem to be completely explained by differences in the age of participants as a large amount of heterogeneity (I^2 > 50%) is still present for these outcomes for adults.
- We performed a subgroup analysis combining two open-label studies (de Silva 1996; Heller 1995) compared with a double-blinded study (Mattson 1985).
  - Considering time to treatment failure for any reason related to the treatment, in the open-label studies (179 participants), the pooled HR is 2.92 (95% CI 1.69 to 5.03, P = 0.0001, I^2= 0%) and in the double-blind study (320 participants), the HR is 1.31 (95% CI 0.95 to 1.81, P = 0.09). There is statistically significant evidence of an interaction between presence of blinding (open-label design versus double-blind design) and treatment effect (test of subgroup differences: P = 0.01, I^2 = 83.6%, Analysis 1.9).
  - Considering time to treatment failure due to adverse events, in the open-label studies (179 participants), the pooled HR is 6.25 (95% CI 2.75 to 14.22, P < 0.0001, I^2 = 0%) and in the double-blind study (320 participants), the HR is 1.51 (95% CI 1.00 to 2.28, P = 0.05). There is statistically significant evidence of an interaction between presence of blinding (open-label design versus double-blind design) and treatment effect (test of subgroup differences: P = 0.002, I^2 = 89.1%, Analysis 1.10).
  - In other words, a significant advantage is observed for phenytoin in the open-label trials (i.e. treatment failure for any reason or due to adverse events occurs later on phenytoin than phenobarbitone, but we are unsure of the magnitude of this advantage as the confidence intervals around the effect size are wide). In the double-blind trial, there was no statistically significant difference between the treatments in terms of treatment failure for any reason related to the treatment but a significant advantage for phenytoin in terms of treatment failures due to adverse events (i.e. treatment failure due to adverse events occurs later on phenytoin than phenobarbitone).
  - The heterogeneity present within the analyses of these outcomes seems to be explained by the differences in treatment effect in the open-label and the double-blinded studies. Important differences in treatment effect in open-label and double-blinded epilepsy monotherapy studies have

also been observed in other reviews in our series of pair-wise reviews for monotherapy in epilepsy (Nevitt 2018a; Nevitt 2018d).

Sensitivity analysis

We conducted sensitivity analyses to investigate misclassification of seizure type, following reclassification of the 33 participants aged 30 or older in Heller 1995 with new onset generalised seizures reclassified to focal onset seizures or an uncertain seizure type (see Sensitivity analysis for further details). For the outcomes, 'Time to treatment failure (any reason related to treatment)' and 'Time to treatment failure due to adverse events,' following sensitivity analysis, results were numerically similar and conclusions were unchanged (i.e. a statistically significant advantage for phenytoin over phenobarbitone was observed for all participants, for individuals with focal onset seizures and for individuals with generalised onset seizures but we are uncertain of the magnitude of the advantage for phenytoin, particularly for individuals with generalised onset seizures). Heterogeneity remained within analysis for all participants (I^2 between 44% and 59%) and for individuals with focal onset seizures (I^2 between 53% and 79%) and there was no evidence of an interaction between epilepsy type (focal onset versus generalised onset) and treatment effect following sensitivity analysis (see Table 5 for all sensitivity analysis results).

We also conducted sensitivity analysis including only the 19 participants randomised in de Silva 1996 before the phenobarbitone arm was discontinued due to adverse events (see Sensitivity analysis for further details). For the outcomes, 'Time to treatment failure (any reason related to treatment)' and 'Time to treatment failure due to adverse events,' following sensitivity analysis, results were quite numerically similar and conclusions were unchanged (as above). However, following this sensitivity analysis, heterogeneity was greatly reduced in analyses for all participants (from $I^2 > 50\%$ in both analyses to $I^2 = 21\%$ and 4% respectively) and for individuals with focal onset seizures ($I^2 = 53\%$ reduced to 0% and $I^2 = 73\%$ reduced to 27% respectively). There was no evidence of an interaction between epilepsy type (focal onset versus generalised onset) and treatment effect following sensitivity analysis (see Table 5 for all sensitivity analysis results).

Considering time to treatment failure due to lack of efficacy, for all of the sensitivity analyses, results were numerically similar and conclusions were unchanged (see Table 5).

Secondary outcomes

Time to first seizure

For this outcome, an HR less than 1 indicates a clinical advantage for phenobarbitone.

Time to first seizure after randomisation was available for 624 individuals in all five trials supplying IPD (98.3% of 635 participants from de Silva 1996; Heller 1995; Mattson 1985; Ogunrin 2005; Pal 1998 and 78.2% of the total 798 participants from the seven included trials). Dates of seizure recurrence were not available for seven participants in Mattson 1985 and four participants in Pal 1998, therefore, we did not include these 14 participants in the analysis. Three hundred and sixty-three out of 624 participants (58%), experienced seizure recurrence, 142 out of 281 (51%), on phenobarbitone and 221 out of 343 (64%) on phenytoin. The overall pooled HR (for 624 participants) was 0.85 (95% CI 0.69 to 1.06, P = 0.14, moderate-certainty evidence, Analysis 1.11), indicating a potential advantage to phenobarbitone which was not statistically significant; in other words, seizure recurrence may occur earlier on phenytoin than phenobarbitone, but we cannot rule out an advantage to phenytoin or no difference between the drugs. There was no evidence of any statistical heterogeneity between trials ($I^2 = 0\%$).

Subgroup analyses: seizure type (focal versus generalised onset)

For participants with focal seizures (463 from five trials), the pooled HR was 0.81 (95% CI 0.63 to 1.04, P = 0.10, I^2=0%, moderate-certainty evidence) indicating a potential advantage to phenobarbitone which was not statistically significant; in other words, seizure recurrence may occur earlier on phenytoin than phenobarbitone, but we cannot rule out an advantage to phenytoin or no difference between the drugs.
For participants with generalised seizures (161 from four trials), the pooled HR was 1.06 (95% CI 0.70 to 1.62 , P = 0.79, I^2=27%, moderate certainty evidence) indicating no clear advantage for either drug. There was no evidence of an interaction between epilepsy type (focal onset versus generalised onset) and treatment effect (test of subgroup differences: P = 0.28, $I^2 = 14.4\%$; Analysis 1.12).

Overall, the pooled HR (adjusted for seizure type) is 0.87 (95% CI 0.70 to 1.08, P = 0.21, moderate-certainty evidence) indicating a potential advantage to phenobarbitone which was not statistically significant.

Sensitivity analysis

In the sensitivity analyses including only the 19 participants randomised in de Silva 1996 before the phenobarbitone arm was discontinued due to adverse events and to investigate misclassification of seizure type, following reclassification of the 46 participants aged 30 or older in Heller 1995 and Ogunrin 2005 with new onset generalised seizures reclassified to focal onset seizures or an uncertain seizure type (see Sensitivity analysis for further details), results were very similar and conclusions were unchanged (see Table 5).

Time to 12-month remission

For this outcome, an HR less than 1 indicates a clinical advantage for phenytoin.

Time to 12-month remission was available for 588 individuals from four out of the five trials supplying IPD

(98.2% of 599 participants from de Silva 1996; Heller 1995; Mattson 1985; Pal 1998 and 73.7% of the total 798 participants from the seven included trials). Dates of seizure recurrence were not available for seven participants in Mattson 1985 and four participants in Pal 1998, therefore, we did not include these 14 participants in the analysis and Ogunrin 2005 was a trial of 12-week duration, therefore 'time to 12-month remission' could not be calculated for this trial. Two hundred and forty-nine out of 588 participants (42%) achieved 12-month remission, 91 out of 263 (34%), on phenobarbitone and 158 out of 325 (49%) on phenytoin. The overall pooled HR (for 588 participants) was 0.90 (95% CI 0.69 to 1.18, P = 0.44, moderate-certainty evidence, Analysis 1.13), indicating no clear advantage between the drugs. There was no evidence of any important statistical heterogeneity between trials (I^2 = 0%).

Subgroup analyses: seizure type (focal versus generalised onset)

The length of follow-up in Pal 1998 was 12 months and only 19 of the original 94 participants in the trial completed 12 months of follow-up and of these 19 participants, only eight (one generalised seizures, seven focal seizures) achieved 12-month remission. Therefore, the HR estimate for individuals with focal seizures in Pal 1998 is based on small numbers and the HR for individuals with generalised seizures is not estimable as only one participant had a event (see Analysis 1.14).

For participants with focal seizures (458), the pooled HR was 0.96 (95% CI 0.70 to 1.33, P = 0.82, I^2= 9%, moderate-certainty evidence) indicating no clear advantage for either drug. For participants with generalised seizures (130), the pooled HR was 0.77 (95% CI 0.46 to 1.28 , P = 0.31, I^2 = 0%, moderate-certainty evidence) indicating a potential advantage for phenytoin, which is not statistically significant; in other words, 12-month remission may occur earlier on phenytoin compared to phenobarbitone but we cannot rule out an advantage to phenobarbitone or no difference between drugs. There was no evidence of an interaction between epilepsy type (focal onset versus generalised onset) and treatment effect (test of subgroup differences: P = 0.47, I^2 = 0%; Analysis 1.14).

Overall, the pooled HR (adjusted for seizure type) is 0.90 (95% CI 0.69 to 1.19, P = 0.46, moderate-certainty evidence) indicating no clear advantage for either drug.

Sensitivity analysis

In the sensitivity analyses including only the 19 participants randomised in de Silva 1996 before the phenobarbitone arm was discontinued due to adverse events and to investigate misclassification of seizure type, following reclassification of the 33 participants aged 30 or older in Heller 1995 with new onset generalised seizures reclassified to focal onset seizures or an uncertain seizure type (see Sensitivity analysis for further details), results were very similar and conclusions were unchanged (see Table 5).

Time to six-month remission

For this outcome, an HR less than 1 indicates a clinical advantage for phenytoin.

Time to six-month remission was available for 588 individuals from four out of the five trials supplying IPD (98.2% of 599 participants from de Silva 1996; Heller 1995; Mattson 1985; Pal 1998 and 73.7% of the total 798 participants from the seven included trials). Dates of seizure recurrence were not available for seven participants in Mattson 1985 and four participants in Pal 1998, therefore, we did not include these 14 participants in the analysis and Ogunrin 2005 was a trial of 12-week duration, therefore 'time to six-month remission' could not be calculated for this trial. Three hundred and eleven out of 588 participants (53%) achieved six-month remission, 122 out of 263 (46%), on phenobarbitone and 189 out of 325 (58%) on phenytoin. The overall pooled HR (for 588 participants) was 0.93 (95% CI 0.73 to 1.18, P = 0.53, moderate-certainty evidence, Analysis 1.15), indicating no clear advantage between the drugs. There was no evidence of any important statistical heterogeneity between trials (I^2 = 21%).

Subgroup analyses: seizure type (focal versus generalised onset)

For participants with focal seizures (458), the pooled HR was 0.94 (95% CI 0.71 to 1.25, P = 0.69, I^2 = 0%, moderate-certainty evidence) indicating no clear advantage for either drug. For participants with generalised seizures (130), the pooled HR was 0.82 (95% CI 0.52 to 1.29 , P = 0.39, I^2=30%, moderate-certainty evidence) indicating a potential advantage for phenytoin, which is not statistically significant; in other words, six-month remission may occur earlier on phenytoin compared to phenobarbitone but we cannot rule out an advantage to phenobarbitone or no difference between drugs. There was no evidence of an interaction between epilepsy type (focal onset versus generalised onset) and treatment effect (test of subgroup differences: P = 0.60, I^2 = 0%; Analysis 1.16).

Overall, the pooled HR (adjusted for seizure type) is 0.91 (95% CI 0.71 to 1.15, P = 0.43, moderate-certainty evidence) indicating no clear advantage for either drug.

Sensitivity analysis

In the sensitivity analyses including only the 19 participants randomised in de Silva 1996 before the phenobarbitone arm was discontinued due to adverse events and to investigate misclassification of seizure type, following reclassification of the 33 participants aged 30 or older in Heller 1995 with new onset generalised seizures reclassified to focal onset seizures or an uncertain seizure type (see Sensitivity analysis for further details), results were very similar and conclusions were unchanged (see Table 5).

In Mattson 1985, there is evidence that the proportional hazards assumption of the Cox regression model is violated (see Data synthesis); the P value of time varying covariate is 0.013 and from visual inspection of the survival plot (Figure 16), the curves cross and hazards become non-proportional around 300 days. In other words, it appears that the treatment effect is not constant throughout follow-up, and this change seems to happen at around 300 days. As Mattson 1985 provides over half of the data contributing to this outcome, sensitivity analysis was performed for all participants by analysing separately those who achieved six-month remission of seizures before and after 300 days using a piecewise Cox regression model is fitted to investigate any change in treatment effect over time, assuming proportional hazards within each interval.

The follow-up period of the four trials is split into two intervals (0 to 300 days and after 300 days) and separate HRs can be estimated for each interval in each trial. Seventy-four (13%) out of 588 participants achieved six-month remission of seizures after 300 days (20 from de Silva 1996, 30 from Heller 1995, 24 from Mattson 1985 and none from Pal 1998).

For interval 0 to 300 days (237 events from 588 participants at risk), the pooled HR was 1.03 (95% CI 0.79 to 1.34, P = 0.85, I^2=0%, Analysis 1.17), suggesting no clear advantage to either drug.

For interval after 300 days (74 events in 113 participants at risk), the pooled HR was 0.78 (95% CI 0.60 to 1.00, P=0.05, I^2 = 19%, Analysis 1.17), indicating a statistically significant advantage to phenytoin.

In other words, in terms of 'early' remissions up to 300 days there appears to be no difference between drugs but 'later' remission may occur significantly earlier on phenytoin than phenobarbitone. However, care is needed with interpretation as these results may be influenced by the smaller number of participants at risk at later time points and by the treatment failure and withdrawal rates from the drugs (see results of Primary Outcome 'Time to treatment failure' (retention time)).

Discussion

Summary of main results

Results for the primary outcome 'time to treatment failure for any reason related to treatment', in addition to the outcomes 'time to treatment failure due to adverse events' and 'time to treatment failure due to lack of efficacy' suggest a statistically significant advantage to phenytoin over phenobarbitone for 499 participants from three trials; in other words, treatment failure may occur significantly earlier on phenobarbitone than phenytoin. This advantage is observed for all participants, for the subgroup of individuals with focal onset seizures and for the subgroup of individuals with generalised onset seizures. There may be an interaction between epilepsy type (focal onset versus generalised onset) and treatment effect, i.e. the treatment effect of phenytoin over phenobarbitone may be larger for individuals with generalised onset seizures compared to individuals with generalised onset seizures. However, the results and the subgroup analyses for 'time to treatment failure for any reason related to treatment' and 'time to treatment failure due to adverse events' are confounded by large amounts of heterogeneity present overall and for individuals with focal onset seizures and we are uncertain of the magnitude of the advantage for phenytoin due to wide confidence intervals around the pooled treatment effect for all outcomes, particularly for individuals with generalised onset seizures.

Additional sensitivity and subgroup analyses and sensitivity analyses show that misclassification of seizure type does not appear to have impacted on the results and that there appears to be an interaction between the age of the participants and treatment effect (the advantage to phenytoin seems to be significantly larger for children compared to adults), but the age of the participants in the included trials does not seem to explain the observed heterogeneity.

On the other hand, there also appears to be an interaction between the presence of blinding in the studies and treatment effect and the heterogeneity present within the analyses does seem to be explained by the differences in treatment effect in the open-label and the double-blinded studies. An additional source of heterogeneity also seems to be a paediatric trial in which the phenobarbitone arm was withdrawn from the trial due to concerns over adverse events.

All of these factors may have confounded the results of our primary analyses in this review and therefore results should be interpreted with caution.

Results for secondary outcomes indicate that for all participants, considering time to first seizure post-randomisation, seizure recurrence may occur earlier on phenytoin than phenobarbitone, but we cannot rule out an advantage to phenytoin or no difference between the drugs. There was no clear differences between the drugs in terms of time to 12-month and six-month remission. Results were similar when considering subgroups of individuals with focal onset seizures and subgroups of individuals with generalised onset seizures, and following sensitivity analyses of secondary outcomes, results were numerically similar and conclusions unchanged.

However, confidence intervals around summary estimates are relatively wide for secondary outcomes and do not suggest equivalence. Furthermore, secondary outcomes may have been confounded by the significantly higher treatment failure rate and significantly earlier time to treatment failure of phenobarbitone compared to phenytoin. Therefore, as for the primary analysis in this review, results should be interpreted with caution.

Overall completeness and applicability of evidence

We have gratefully received individual participant data (IPD) for 635 individuals (80% of individuals from all

eligible trials), from the authors of five trials (de Silva 1996; Heller 1995; Mattson 1985; Ogunrin 2005; Pal 1998), which included a comparison of phenobarbitone with phenytoin for the treatment of epilepsy. We could not include 163 individuals (20%) from the other two relevant trials (Czapinski 1997; Thilothammal 1996), in any analysis, as IPD were not available and the published reports did not report outcomes of interest.

While we received IPD for 635 participants, we were not able to include all data in all of our analyses. Because of the short, three-month duration of the trial, we were unable to include 36 participants from Ogunrin 2005 in our remission analyses, and in this short follow-up time, no participants withdrew from treatment; therefore, this trial could not contribute to our primary outcome of 'time to treatment failure' either. We were also unable to include 110 participants from Pal 1998 in analyses of treatment failure as treatment failure information was not available. Therefore, our primary outcome was, in fact, based on 499 participants (63% of individuals from all eligible trials).

Having to exclude data for between 20% and 40% of the eligible participants due to lack of IPD and insufficient reporting in trial publications was likely to have had an impact on the applicability of the evidence; therefore, we encourage caution in the interpretation of all results in this review. However, it was difficult to quantify exactly how large this impact was on the results of this review (see Potential biases in the review process).

Three trials contributing around 73% of the participant data to this review recruited adults only (Heller 1995; Mattson 1985; Ogunrin 2005); the other two trials contributing around 27% of data were paediatric trials (de Silva 1996; Pal 1998). Also, the largest single trial contributing over a third of the participant data to this review, Mattson 1985, recruited individuals with focal onset seizures only and recruited participants who were described as "untreated" or "undertreated." It was unclear how many participants were "undertreated" and how "undertreated" was defined in the study; i.e. it is unclear whether it be assumed that participants with no prior treatment and a small amount of prior treatment are clinically similar.

Only 26% of participants included in this review were experiencing generalised onset seizures, which is reflected in the confidence intervals around summary effect sizes for individuals with generalised onset seizures, which are much wider than within the analyses of individuals wit focal onset seizures. Furthermore, there is evidence within this review to suggest that up to 28% of individuals with newly onset generalised seizures may have had their seizure type misclassified. For these reasons, the results of this review may not be fully generalisable to children or to individuals with generalised onset seizures, and more evidence recruiting these types of participants is required.

Ogunrin 2005 classified generalised and focal onset seizures according to the International League Against Epilepsy (ILAE), classification of 1981 (Commission 1981), rather than the revised ILAE classification in 1989 (Commission 1989), which may have led to misclassification. Furthermore, Ogunrin 2005 was conducted in Nigeria, a lower middle-income country without access to the same facilities as trials conducted in the USA and Europe; therefore, seizure types were classified clinically, and electroencephalographics (EEGs)/magnetic resonance images (MRIs), were not required for diagnosis of epilepsy. Clinical classification may also have contributed to potential misclassification in this trial.

In three of the five trials (de Silva 1996; Heller 1995; Pal 1998), participants and personnel were unblinded to treatment allocation (outcome assessors were blinded in Pal 1998). It is however, debatable whether double-blind design is the most appropriate for trials of monotherapy in epilepsy of long duration, and whether such a design does have an impact upon the dropout rate, and therefore, the results of the trial. The authors of the three unblinded trials state that blinding would not have been "practical" or "ethical" and would have resulted in a large withdrawal rate as blinding does not conform to standard clinical practice of increasing drug doses to therapeutic ranges (Heller 1995). This effect is demonstrated by the unblinded study (Heller 1995) with a 29% treatment withdrawal rate (34 out of 116 participants withdrew from treatment, 40% from phenobarbitone and 20% from phenytoin) and the blinded study (Mattson 1985) with a 48% treatment withdrawal rate (152 out of 320 participants withdrew from treatment, 51% from phenobarbitone and 44% from phenytoin). The unblinded study (de Silva 1996) had a treatment withdrawal rate of 40% (25 out of 63 participants), however, this rate is influenced by the high withdrawal rate of phenobarbitone (eight out of 10 (80%) participants withdrew from phenobarbitone while 17 out of 53 (32%) withdrew from phenytoin).

As further discussed in Summary of main results, the differences between the open-label and double-blinded studies, suggests a potential explanation for the heterogeneity observed; clinicians, particularly clinicians in the UK, may have a prior opinion of particular anti-epileptic drugs and may expect adverse effects from phenobarbitone and would therefore be more likely to withdraw participants from this drug in an unblinded trial. Further, it is interesting to note that the UK trial recruiting children (de Silva 1996) suspended randomisation to phenobarbitone due to serious adverse effects after 10 children had been randomised to that drug, whereas this problem was not reported in a trial recruiting children conducted in India (Pal 1998), in which phenobarbitone is concluded to be an "effective and acceptable antiepileptic drug for rural Indian children." These two studies may have been conducted from different perspectives due to the country of recruitment; de Silva 1996 in the UK where concerns had been raised over the suitability of drugs such as phenobarbitone due to documented cases of adverse effects and Pal 1998 in rural India where income is limited, newer generation antiepileptic drugs (AEDs) are not readily available or affordable and therefore, drugs such as phenobarbitone are more likely to be used. We note the influence of country of recruitment

over the methodological design and perhaps the results of the trial. Within the USA and Europe, where many treatment options are available, phenobarbitone is no longer considered to be a first-line agent, in favour of more tolerable first-line agents, such as carbamazepine and lamotrigine (NICE 2012), whereas in low- and middle-income countries or rural regions, where income is limited and newer generation antiepileptic drugs are not readily available or affordable, older and cheaper drugs, such as phenobarbitone, are more likely to be used as comparators.

As described in Summary of main results, results of this review are likely to be confounded by heterogeneity in design and methodological inadequacies of the included trials. Therefore, this apparent association may not be a true association and all results of this review should be interpreted with caution. We would not advocate basing a choice between these two drugs on the results of this review alone.

Quality of the evidence

The five trials for which IPD were made available were generally of relatively good methodological quality; however, three out of the five trials for which we received IPD were at high risk of bias for at least one aspect (see Figure 3), which may have introduced bias into analyses. Three of the trials contributing 47% of the participant data to this review described adequate methods of randomisation and allocation concealment (de Silva 1996; Heller 1995; Ogunrin 2005); however, the other two largest single trials contributing 53% of participant data to this review did not describe the method of randomisation or allocation concealment used, or both, and this information was not available from trial authors (Mattson 1985; Pal 1998). We are uncertain whether this lack of information has affected the results of this review. As further discussed in Summary of main results and Overall completeness and applicability of evidence, the differences in design of the trials with respect to blinding was likely to have impacted on the results of the primary outcome 'time to treatment failure', and in turn, the treatment failure rates may have impacted on the secondary efficacy outcomes of time to first seizure and time to 12-month and six-month remission.

Trials for which no IPD were available were generally of poorer quality than those for which we received IPD (Czapinski 1997; Thilothammal 1996), particularly Czapinski 1997, which was available only in abstract form and provided only very limited information on trial methodology

Overall, due to the documented methodological issues that may have introduced heterogeneity, biases and imprecision into our meta-analyses, we rated the evidence provided in this review as low quality (certainty) for our primary outcome and moderate quality (certainty) for our secondary outcomes according to GRADE criteria (See Summary of findings table 1 and Summary of findings table 2), and would not advocate use of the evidence in this review for clinical decision-making between the two drugs.

Potential biases in the review process

We were able to include IPD for 635 out of 798 eligible participants (80%), from five out of seven trials in this review and conducted all analyses as IPD analyses. Such an approach has many advantages, such as allowing the standardisation of definitions of outcomes across trials, and attrition and reporting biases are reduced, as we can perform additional analyses and calculate additional outcomes from unpublished data. For the outcomes we used in this review that are of a time-to-event nature, an IPD approach is considered to be the 'gold standard' approach to analysis (Parmar 1998).

However, despite the advantages of this approach, for reasons out of our control, we were not able to obtain IPD for 163 participants from two eligible trials, and no aggregate data were available for our outcomes of interest in trial publications. We therefore had to exclude 20% of eligible participants from our analyses, which may have introduced bias into the review. Given that no statistically significant differences were found between the drugs in terms of proportions of participants seizure-free and proportions of participants withdrawing from allocated treatment in the two trials for which IPD were not available (where recorded, see Table 2), we do not believe that our conclusions would have changed for the outcomes of this review had the IPD for the seven trials been available. We do however, recommend caution when interpreting results of analyses of this review because of potential retrieval bias from the exclusion of 20% of eligible participants from two trials in this review.

We made some assumptions in the statistical methodology used in this review. Firstly, when we received only follow-up dates and seizure frequencies, we used linear interpolation to estimate seizure times. We are aware that an individual's seizure patterns may be non-linear; therefore, we recommend caution when interpreting the numerical results of the seizure-related outcomes. We also made an assumption that treatment effect for each outcome did not change over time (proportional hazards assumption, see Data synthesis). We are aware that in trials of long duration (e.g. de Silva 1996, Heller 1995 and Mattson 1985 followed up participants for between three and 10 years), the assumption of treatment effect remaining constant over time may not be appropriate. For example, there is likely to be a difference between participants who achieve immediate remission compared with participants who achieve later remission, and we encourage that results should be interpreted with this limitation in mind.

Agreements and disagreements with other studies or reviews

To our knowledge, together with previous versions of this review, this is the only systematic review and meta-analysis that compares phenobarbitone and carbamazepine monotherapy for focal onset seizures and generalised onset tonic-clonic seizures. A network meta-analysis has been published (Nevitt 2017a),

comparing all direct and indirect evidence from phenobarbitone, phenytoin, and other standard and new antiepileptic drugs licensed for monotherapy. The results of this review generally agree with the results of the network meta-analysis; results of this network meta-analysis showed a statistically significant advantage for phenytoin compared with phenobarbitone for 'time to treatment failure' for participants with focal onset seizures and no statistically significant differences were found between the drugs for participants with generalised onset seizures or for any of the secondary outcomes.

Authors' conclusions

Implications for practice

Current UK guidelines recommend carbamazepine or lamotrigine as first-line treatment for adults and children with new onset focal seizures and sodium valproate for adults and children with new onset generalised seizures (NICE 2012). Results of this review do not refute or support these guidelines.

The results of this review do not provide evidence on which a choice can be made between phenytoin and phenobarbitone with respect to seizure control. Phenytoin is significantly less likely to be failed as a treatment, which may make it the preferred choice of the two drugs compared in this review.

However, as the trials contributing to the analyses had methodological inadequacies and inconsistencies, particularly trial design differences, with respect to blinding, which may have had an impact on the certainty of the evidence provided by this review. Therefore, we do not suggest that results of this review alone should form the basis of a treatment choice for a patient with newly onset seizures. We encourage caution in the use of these drugs in women of child-bearing potential because of documented teratogenic effects, where the risk is estimated to be two to three times that of the general population (Bromley 2014; Meador 2008; Morrow 2006; Weston 2016).

Implications for research

Few consistent differences in efficacy have been found between these two commonly used antiepileptic drugs in individual trials. The methodological quality of trials comparing these two drugs has been variable, producing variable individual trial results introducing heterogeneity into the pooled results of this review and therefore making the pooled results difficult to interpret. If there are differences in efficacy and tolerability across heterogeneous populations of individuals such as those studied here, it is likely that these differences are small. It has been argued that future comparative antiepileptic drug trials should be powered to establish equivalence (Jones 1996), and therefore be capable of detecting what is considered to be the smallest important clinical difference.

This review highlights the need for the design of future antiepileptic drug monotherapy trials that recruit individuals with specific epilepsy syndromes to be powered to detect a difference between particular antiepileptic drugs. An approach likely to reflect and inform clinical practice, as well as being statistically powerful, would be to recruit heterogeneous populations for whom epilepsy syndromes have been adequately defined, with testing for interaction between treatment and epilepsy syndrome. In view of potential problems of misclassification, syndromes will have to be well-defined, with adequate checking mechanisms to ensure that classifications are accurate and a system to recognise uncertainty surrounding epilepsy syndromes in individuals within trials. It is also important that future trials are of a sufficient duration to measure long-term effectiveness of antiepileptic drugs (treatments that will be life-long for many individuals with epilepsy), as well as psychosocial, quality-of-life and health economic outcomes.

Consideration is also required in the design of a trial regarding whether to blind participants and outcome assessors to treatment allocation. While an open-label design is a more pragmatic and practical approach for large long-term trials, when trials involve drugs with documented adverse-event profiles, such as phenobarbitone, masking of treatment may be important to avoid preconceptions of the drug being more likely to be associated with serious adverse events, which the results of this review did not show.

The choice of outcomes at the design stage of a trial and the presentation of the results of outcomes, particularly of a time-to-event nature, require very careful consideration. While the majority of trials of a monotherapy design record an outcome measuring efficacy (seizure control), and an outcome measuring tolerability (adverse events), there is little uniformity between the definition of the outcomes and the reporting of the summary statistics related to the outcomes (Nolan 2013a), making an aggregate data approach to meta-analysis in reviews of monotherapy trials impossible. Where trial authors cannot or will not make individual participant data (IPD), available for analysis, we are left with no choice but to exclude a proportion of relevant evidence from the review, which will impact upon the interpretation of results of the review and applicability of the evidence and conclusions. The International League Against Epilepsy recommends that trials of a monotherapy design should adopt a primary effectiveness outcome of 'time to treatment failure (retention time)' and should be of a duration of at least 48 weeks to allow for assessment of longer-term outcomes, such as remission (ILAE 1998; ILAE 2006). If trials followed these recommendations, an aggregate data approach to meta-analysis may be feasible, reducing the resources and time required from an IPD approach.

A network meta-analysis has also been published (Nevitt 2017a), comparing all direct and indirect evidence from phenobarbitone, phenytoin, and other standard and new antiepileptic drugs licensed for monotherapy. This

network meta-analysis will be updated as more information becomes available; however, we acknowledge that as both phenobarbitone and phenytoin are no longer considered to be a first-line agent for newly diagnosed individuals, in favour of newer agents, such as lamotrigine and levetiracetam, it is unlikely that a substantial amount of new evidence will become available for this review.

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We acknowledge Steven Taylor as lead investigator on the original review and Paula Williamson for contributions to the original review.

We acknowledge Jennifer Weston for contributions to previous versions of the review.

Contributions of authors

SJ Nevitt assessed trials for inclusion in the review update, obtained individual participant data from trial investigators for the review update, assessed risk of bias in all included trials, performed analyses in Stata version 14, added survival plots and a 'Summary of findings' table, and updated the text of the review.

C Tudur Smith was the lead investigator on the original review, assessed eligibility and methodological quality of original individual trials, organised and cleaned the IPD sets, performed data validation checks and statistical analyses, and co wrote the original review.

AG Marson obtained IPD from trial investigators, provided guidance with the clinical interpretation of results, assessed eligibility and methodological quality of individual trials, and co-wrote the original review.

Declarations of interest

Sarah J Nevitt: none known.

Anthony G Marson: a consortium of pharmaceutical companies (GSK, EISAI, UCB Pharma) funded the National Audit of Seizure Management in Hospitals (NASH) through grants paid to University of Liverpool. Professor Tony Marson is Theme Leader for Managing Complex Needs at NIHR CLAHRC NWC.

Catrin Tudur Smith: none known.

Differences between protocol and review

December 2014: the title was changed to specify that the review uses individual participant data (IPD).

Update 2015: we added sensitivity analyses following identification of potential misclassification of seizure type. The existence of misclassification in the individual studies could not have been known at the time of writing the original protocol.

Update 2015: we added the outcomes 'time to six-month remission' and 'adverse events' for consistency with the other reviews in the series of Cochrane IPD reviews investigating pair-wise monotherapy comparisons.

Update 2015: we added 'Summary of findings' tables to the update in 2015 and added text in the Methods section for 'Summary of findings' tables in August 2016.

Update 2019: we changed the title in line with the titles of other pair-wise monotherapy comparisons in the series (i.e. 'monotherapy for epilepsy' instead of 'for focal onset seizures and generalised onset tonic-clonic seizures).

'Time to withdrawal of allocated treatment' was re-defined as 'Time to treatment failure' due to feedback received from the Cochrane Editorial Unit regarding potential confusion regarding 'withdrawal' as a positive or negative outcome of antiepileptic monotherapy.

Additional analyses of 'Time to treatment failure' (due to lack of efficacy and due to adverse events), following feedback on published antiepileptic drug monotherapy reviews that these sub-outcomes would be useful for clinical practice.

The term 'partial' has been replaced by 'focal', in accordance with the most recent classification of epilepsies of the International League Against Epilepsy (Scheffer 2017).

Cross-over designs have been excluded as this design is not appropriate for measuring the long-term outcomes of the review; previously included cross-over studies now excluded from the review.

Published notes

Sarah J Nolan (lead author of 2013 update) is now Sarah J Nevitt

Characteristics of studies

Characteristics of included studies

Czapinski 1997

Methods	36-month randomised comparative study. Method of generation of random list and allocation concealment not stated.
Participants	Adults with newly diagnosed epilepsy. Number randomised: PB = 30; PHT = 30. 100% focal epilepsy, Age range: 18 to 40 years. Percentage male and range of follow-up not mentioned.
Interventions	Monotherapy with PB or PHT. Starting doses PHT = 200 mg/day, PB = 100 mg/day. Dose achieved not stated.
Outcomes	Proportion achieving 24-month remission at 3 years and exclusions after randomisation due to adverse effects or no efficacy.
Notes	Abstract only. Outcomes chosen for this review were not reported. Contact made with study authors who agreed to provide IPD, but IPD was never received.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study "randomised" but no further information provided
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding (performance bias and detection bias)	Unclear risk	No information provided
Incomplete outcome data (attrition bias)	Unclear risk	"Exclusion rates" (interpreted as withdrawal rates) reported for all treatment groups, no further information provided
Selective reporting (reporting bias)	Unclear risk	No protocol available and study reported only in abstract form, outcomes for this review not available
Other Bias	Unclear risk	Insufficient detail provided in abstract to allow judgement

de Silva 1996

Methods	Random list generated using random permuted blocks. Allocation concealed using sealed opaque envelopes. Unblinded.
Participants	Children with newly diagnosed epilepsy (two or more untreated focal or generalised tonic clonic seizures in the 12 months preceding the study). Number randomised: PB group = 10; PHT group = 54. 38 children (59%) with focal epilepsy. 35 (55%) male children. Mean age (range): 9 (3 to 16) years. Range of follow-up 3 to 88 (months).
Interventions	Monotherapy with PB or PHT. Median daily dose achieved: PB = not stated due to withdrawal of treatment; PHT = 175 mg/day.
Outcomes	Time to first seizure recurrence after start of therapy. Time to 12-month remission from all seizures. Adverse effects and withdrawals due to adverse events.
Notes	6 of the first 10 children assigned to PB had unacceptable adverse effects so no further children were assigned to PB. IPD provided for all outcomes of this review.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation list generated using permuted blocks of size 8 or 16 with stratification for centre, seizure type and presence of neurological signs
Allocation concealment (selection bias)	Low risk	Allocation concealed via 4 batches of concealed opaque envelopes
Blinding (performance bias and detection bias)	High risk	Unblinded, authors state masking of treatment would not be “practicable or ethical” and would “undermine compliance.” Lack of masking could have led to early withdrawal of PB from the trial.
Incomplete outcome data (attrition bias)	Low risk	Attrition rates reported, all randomised participants analyses from IPD provided[a]
Selective reporting (reporting bias)	Low risk	All outcomes reported or calculated with IPD provided[a]
Other Bias	Low risk	None identified

Heller 1995

Methods	Random list generated using random permuted blocks. Allocation concealed using sealed opaque envelopes. Unblinded.
Participants	Adults with newly diagnosed epilepsy (two or more untreated focal or generalised tonic clonic seizures in the 12 months preceding the study). Number randomised: PB group = 58; PHT group = 63. 53 participants (44%) with focal epilepsy. 59 (49%) male participants. Mean age (range): 34 (14 to 77) years. Range of follow-up 1 to 91 (months).
Interventions	Monotherapy with PB or PHT. Median daily dose achieved: PB = 105 mg/day; PHT = 300 mg/day.
Outcomes	Time to first seizure recurrence after start of therapy. Time to 12-month remission from all seizures. Adverse effects and withdrawals due to adverse events.
Notes	IPD provided for all outcomes of this review.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation list generated using permuted blocks of size 8 or 16 with stratification for centre, seizure type and presence of neurological signs
Allocation concealment (selection bias)	Low risk	Allocation concealed via 4 batches of concealed opaque envelopes
Blinding (performance bias and detection bias)	High risk	Unblinded, authors state masking of treatment would not be “practical” and would have quote: “introduced bias due to a very large drop-out rate.” Lack of blinding may have lead to more withdrawals of PB
Incomplete outcome data (attrition bias)	Low risk	Attrition rates reported, all randomised participants analyses from IPD provided[a]
Selective reporting (reporting bias)	Low risk	All outcomes reported or calculated with IPD provided[a]
Other Bias	Low risk	None identified

Mattson 1985

Methods	Multicentre randomised study with separate randomisation schemes used for each seizure type. Method of generation of random list not stated. Allocation concealment achieved with sealed opaque envelopes. Double-blind achieved by providing additional blank tablet.
Participants	Adults with previously untreated or under-treated simple or complex focal or secondary generalised tonic clonic seizures. Number randomised: PB group = 155; PHT group = 165. 100% of participants had focal epilepsy. 88% of participants were male. Mean age (range) 40 (18-81) years. Range of follow-up: 0-66 months.
Interventions	Monotherapy with PB or PHT. Median daily dose achieved: PHT = 400 mg/day; PB = 160 mg/day.
Outcomes	Participant retention/time to drug failure (length of time participant continued to take randomised drug). Composite scores of seizure frequency (seizure rates and total seizure control) and toxicity. Incidence of side effects.
Notes	IPD provided for all outcomes of this review. Proportions of "untreated" and "under treated" not known.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Participants randomised with stratification for seizure type. Method of generation of random list not stated
Allocation concealment (selection bias)	Unclear risk	No information provided in the publication or by study authors
Blinding (performance bias and detection bias)	Low risk	Double-blinded (participants and personnel) using additional blank tablet
Incomplete outcome data (attrition bias)	Low risk	Attrition rates reported, all randomised participants analyses from IPD provided[a]
Selective reporting (reporting bias)	Low risk	All outcomes reported or calculated with IPD provided[a]
Other Bias	Low risk	None identified

Ogunrin 2005

Methods	Double-blinded, parallel-group, randomised trial conducted in a single-centre in Nigeria. 3 treatment arms: carbamazepine, PHT, PB
Participants	Consecutive newly diagnosed participants aged ≥ 14 years presenting at the outpatient neurology clinic of the University Teaching Hopsital, Benin City, Nigeria, with recurrent, untreated afebrile seizures Number randomised: PHT = 18; PB = 18 5 participants with focal seizures (14%) 22 male participants (61%) Mean age (range): 27.1 years (15-55 years) Range of follow-up: all participants followed up for 12 weeks
Interventions	Monotherapy with PB or CBZ. Median daily dose (range): PB = 120 mg (60 mg to 180 mg), Median daily dose (range): PHT = 200 mg (100 mg to 300 mg)
Outcomes	Cognitive measures (reaction times, mental speed, memory, attention)
Notes	We received IPD for all randomised participants. The trial duration was 12 weeks; all participants completed the trial; therefore, we could not calculate the outcomes 'time to treatment failure', 'time to six-month remission', and 'time to 12-month remission'. We calculated 'time to first seizure' from the IPD provided

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The trial randomised participants using simple randomisation: each participant was asked to pick 1 from a table of numbers (1-60); the numbers corresponded to allocation of 1 of 3 drugs (the trial author provided information).
Allocation concealment (selection bias)	Low risk	Recruitment/randomisation of participants and allocations of treatments took place on different sites (the trial author provided information).
Blinding (performance bias and detection bias)	Low risk	Participants were single-blinded. The trial did not blind the research assistant recruiting participants and counselling on medication adherence. Investigators performing cognitive assessments were single-blinded.
Incomplete outcome data (attrition bias)	Low risk	Attrition rates reported, all randomised participants analyses from IPD provided[a]
Selective reporting (reporting bias)	Low risk	We calculated 1 outcome for this review from the IPD provided[a]. Other outcomes for this review were not available because of short trial length. All cognitive outcomes from the trial were well reported.
Other Bias	Low risk	None detected

Pal 1998

Methods	Participants randomised by prepared randomised number list and by minimisation. Method of allocation concealment not stated. Participants (and parents) and personnel unblinded, outcome assessor single blinded.
Participants	Children from a rural district of a developing country (India) who had experienced two or more unprovoked seizures within the 12 months preceding the study and had been untreated in the three months preceding the study. Number randomised: PB group = 47 ; PHT group = 47. 60 children (64%) had focal epilepsy. 49 (52%) male children. Mean age (range): 11(2 to 18) years. ¬Range of follow-up (months) 0-12.
Interventions	Monotherapy with PB or PHT. Maintenance doses: PHT 5 mg/kg/day, PB 3 mg/kg/day. Daily dose achieved not stated.
Outcomes	Time to first seizure. Proportion seizure-free in each study quarter. Proportion of adverse events including behavioural side effects.
Notes	IPD provided for remission and seizure outcomes of this review. Treatment failure information not available.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	First 10 participants randomised from a pre-prepared balanced random number list, following participants randomised by minimisation with stratification by age group and presence of cerebral impairment ¬
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding (performance bias and detection bias)	High risk	Participants, parents and treating physicians unblinded for quote: "practical and ethical reasons." Outcome assessors single-blinded. Withdrawal information from treatments not available, however lack of blinding may have influenced withdrawal rates
Incomplete outcome data (attrition bias)	Low risk	Attrition rates reported, all randomised participants analyses from IPD provided[a]
Selective reporting (reporting bias)	Low risk	All outcomes reported or calculated with IPD provided[a]
Other Bias	Low risk	None identified

Thilothammal 1996

Methods	Random list generated using computer-generated random numbers. Method of concealment not mentioned. Double-blind achieved by providing additional placebo tablets.¬¬¬¬¬¬¬¬¬¬¬¬¬¬¬
Participants	Children with more than one previously untreated generalised tonic clonic (afebrile) seizure. Number randomised: PB group = 51 ; PHT group = 52. 0% focal epilepsy. 55 (53%) male children. Age range: 4 to 12 years. Range of follow-up (months): 22 to 36.
Interventions	Monotherapy with PB or PHT. Dose achieved not stated.
Outcomes	Proportion with recurrence of seizures. Adverse effects/side effects.
Notes	Outcomes chosen for this review were not reported. Original trial authors could not be contacted to request IPD.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants randomised via a computer-generated list of random numbers
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding (performance bias and detection bias)	Low risk	Double-blinded (participants and personnel) using additional placebo tablets
Incomplete outcome data (attrition bias)	Low risk	Attrition rates reported, all randomised participants analysed
Selective reporting (reporting bias)	Low risk	No protocol available, outcomes chosen for this review not reported, main outcomes (seizure reduction and adverse effects) adequately reported
Other Bias	Low risk	None identified

Footnotes

Abbreviations: CBZ: carbamazepine, IPD: individual participant data, PB: phenobarbitone, PHT: phenytoin

a. For studies for which IPD were provided (de Silva 1996, Heller 1995, Mattson 1985, Ogunrin 2005; Pal 1998) attrition and reporting bias are reduced as attrition rates and unpublished outcome data are requested

Characteristics of excluded studies

Bird 1966

Reason for exclusion	Unclear whether trial is randomised and unclear whether participants received PHT or PB as monotherapy.

Cereghino 1974

Reason for exclusion	Cross-over design; cross-over studies are not an appropriate design for measuring the long-term outcomes of interest in this review

Cereghino 1975

Reason for exclusion	Polytherapy comparisons.

Gruber 1962

Reason for exclusion	Cross-over design; cross-over studies are not an appropriate design for measuring the long-term outcomes of interest in this review

Meador 1990

Reason for exclusion	Comparison between PHT and PB monotherapy cannot be made due to the cross-over trial design. Some participants were receiving treatment at the start of the first period which had to be withdrawn slowly.

Verma 2010

Reason for exclusion	Trial recruits neonatal infants with seizures due to birth complications (birth asphyxia) rather than epilepsy.

White 1966

Reason for exclusion	Polytherapy comparisons.

Footnotes

PB: phenobarbitone, PHT: phenytoin

Characteristics of studies awaiting classification

Footnotes

Characteristics of ongoing studies

Footnotes

Summary of findings tables

1 Summary of findings - Phenobarbitone compared with phenytoin for epilepsy (time to treatment failure)

Phenobarbitone compared with phenytoin for epilepsy (time to treatment failure)

Patient or population: adults and children with newly onset focal or generalised epilepsy

Settings: outpatients

Intervention: phenobarbitone

Comparison: phenytoin

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)[a]	No of Participants (studies)	Certainty (quality) of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Phenytoin	Phenobarbitone				
Time to treatment failure (any reason related to treatment) *All participants*[a] Range of follow-up: 0 to 4653 days	The median time to treatment failure was 2135 days in the phenytoin group	The median time to treatment failure was 681 days (1454 days shorter) in the phenobarbitone group	**HR 1.61** (1.22 to 2.12)	499 (3 studies)	⊕⊕⊖⊖ **low**[b,c]	HR<1 indicates a clinical advantage for phenobarbitone Treatment failure due to adverse events (HR 1.99, 95% CI 1.37 to 2.87, P = 0.0003, I^2 = 58%), and due to lack of efficacy (HR 1.87, 95% CI 1.32 to 2.66, P = 0.0005, I^2 = 0%), also occurred significantly earlier on phenobarbitone compared to phenytoin.

Time to treatment failure (any reason related to treatment) *Subgroup: focal onset seizures* Range of follow-up: 0 to 4653 days	The median time to treatment failure was 1300 days in the phenytoin group	The median time to treatment failure was 540 days (760 days shorter) in the phenobarbitone group	**HR 1.46** (1.09 to 1.96)	404 (3 studies)	⊕⊕⊖⊖ **low**[b,c]	HR<1 indicates a clinical advantage for phenobarbitone Treatment failure due to adverse events (HR 1.86, 95% CI 1.27 to 2.73, P = 0.001, I^2=73%), and due to lack of efficacy (HR 1.73 95% CI 1.19 to 2.52, P = 0.004, I^2 = 0%), also occurred significantly earlier on phenobarbitone compared to phenytoin.
Time to treatment failure (any reason related to treatment) *Subgroup: generalised onset seizures* Range of follow-up: 0 to 4272 days	The 10th percentile[d] of time to treatment failure was 778 days in the phenytoin group	The 10th percentile[d] of time to treatment failure was 189 days (589 days shorter) in the phenobarbitone group	**HR 4.04** (1.61 to 10.14)	95 (2 studies)	⊕⊕⊖⊖ **low**[b,e]	HR<1 indicates a clinical advantage for phenobarbitone Treatment failure due to adverse events (HR 4.60, 95% CI 1.17 to 17.98, P = 0.03, I^2=0%), and due to lack of efficacy (HR 3.40, 95% CI 1.21 to 9.54, P = 0.02, I^2 = 0%), also occurred significantly earlier on phenobarbitone compared to phenytoin.

*Illustrative risks in the phenobarbitone and phenytoin groups are calculated at the median time to treatment failure (i.e. the time to 50% of participants failing or withdrawing from allocated treatment) within each group across all trials. The relative effect (pooled hazard ratio) shows the comparison of 'time to treatment failure' between the treatment groups.

CI: 95% confidence interval; **HR**: hazard ratio

GRADE Working Group grades of evidence

High certainty (quality): Further research is very unlikely to change our confidence in the estimate of effect.

Moderate certainty (quality): Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low certainty (quality): Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very certainty (quality): We are very uncertain about the estimate.

Footnotes

a. Pooled HR for all participants adjusted for seizure type. All pooled HRs calculated with fixed effects

b. Downgraded once for risk of bias: risk of bias judged as high for three unblinded studies as lack of masking may have influenced the withdrawal rates of phenobarbitone

c. Downgraded once for inconsistency: Substantial heterogeneity present between studies (I^2 = 53%); when results are repeated with random effects, confidence intervals around pooled results are fairly wide. Inconsistency may be due to combining studies of an open-label and double-blind design.

d. The 10th percentile of time to treatment failure (i.e. the time to 50% of participants failing or withdrawing from allocated treatment) is presented for the subgroup with generalised seizures, as fewer than 50% of participants failed/withdrew from treatment we could not calculate median time.

e. Downgraded once for imprecision: the subgroup of participants with generalised onset tonic-clonic seizures is relatively small (19% of total participants) and confidence intervals around pooled results are fairly wide.

2 Summary of findings - Phenobarbitone compared with phenytoin for epilepsy (secondary outcomes)

Phenobarbitone compared with phenytoin for epilepsy (secondary outcomes)

Patient or population: adults and children with newly onset focal or generalised epilepsy

Settings: outpatients

Intervention: phenobarbitone

Comparison: phenytoin

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)[a]	No of Participants (studies)	Certainty (quality) of the evidence	Comments
	Assumed risk	Corresponding risk				
	Phenytoin	Phenobarbitone				
Time to first seizure (post-randomisation) *All participants*[a] Range of follow-up: 0 to 4589 days	The median time to first seizure post-randomisation was 108 days in the phenytoin group	The median time to first seizure post-randomisation was 186 days (78 days longer) in the phenobarbitone group	**HR 0.87** (0.70 to 1.08)	624 (5 studies)	⊕⊕⊕⊖ **moderate**[b]	HR < 1 indicates a clinical advantage for phenobarbitone
Time to first seizure (post-randomisation) *Subgroup: focal onset seizures* Range of follow-up: 0 to 4589 days	The median time to first seizure post-randomisation was 74 days in the phenytoin group	The median time to first seizure post-randomisation was 116 days (42 days longer) in the phenobarbitone group	**HR 0.81** (0.63 to 1.04)	463 (5 studies)	⊕⊕⊕⊖ **moderate**[b]	HR < 1 indicates a clinical advantage for phenobarbitone
Time to first seizure (post-randomisation) *Subgroup: generalised onset seizures* Range of follow-up: 1 to 4035 days	The median time to first seizure post-randomisation was 322 days in the phenytoin group	The median time to first seizure post-randomisation was 439 days (117 days longer) in the phenobarbitone group	**HR 1.06** (0.70 to 1.62)	161 (4 studies)	⊕⊕⊕⊖ **moderate**[b]	HR < 1 indicates a clinical advantage for phenobarbitone
Time to achieve 12-month remission (seizure-free period) *All participants* Range of follow-up: 0 to 4061 days	The median time to achieve to 12-month remission was 481 days in the phenytoin group	The median time to achieve to 12-month remission was 483 days (2 days longer) in the phenobarbitone group	**HR 0.90** (0.69 to 1.19)	588 (4 studies)	⊕⊕⊕⊖ **moderate**[b]	HR < 1 indicates a clinical advantage for phenytoin
Time to achieve 12-month remission (seizure-free period) *Subgroup: focal onset seizures* Range of follow-up: 0 to 4061 days	The median time to achieve to 12-month remission was 515 days in the phenytoin group	The median time to achieve to 12-month remission was 483 days (32 days shorter) in the phenobarbitone group	**HR 0.96** (0.70 to 1.33)	458 (4 studies)	⊕⊕⊕⊖ **moderate**[b]	HR < 1 indicates a clinical advantage for phenytoin

Time to achieve 12-month remission (seizure-free period) *Subgroup: generalised onset seizures* Range of follow-up: 8 to 3869 days	The median time to achieve to 12-month remission was 375 days in the phenytoin group	The median time to achieve to 12-month remission was 421 days (46 days shorter) in the phenobarbitone group	**HR 0.77** (0.46 to 1.28)	130 (3 studies)[c]	⊕⊕⊕⊖ **moderate**[b]	HR < 1 indicates a clinical advantage for phenytoin

*Illustrative risks in the phenobarbitone and phenytoin groups are calculated at the median time to first seizure or time to 12-month remission (i.e. the time to 50% of participants experiencing a first seizure or 12-months of remission) within each group across all trials. The relative effect (pooled hazard ratio) shows the comparison of 'time to first seizure' or 'time to 12-month remission' between the treatment groups.

CI: 95% confidence interval; **HR**: hazard ratio

GRADE Working Group grades of evidence

High certainty (quality): Further research is very unlikely to change our confidence in the estimate of effect.

Moderate certainty (quality): Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low certainty (quality): Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very certainty (quality): We are very uncertain about the estimate.

Footnotes

a. Pooled HR for all participants adjusted for seizure type. All pooled HRs calculated with fixed effects

b. Downgraded once for risk of bias: risk of bias judged as high for three unblinded studies as lack of masking may have influenced the withdrawal rates of phenobarbitone

c. The HR for individuals with generalised seizures is not estimable from one of the trials as only one participant achieved 12-month remission

Additional tables

1 Demographic characteristics of trial participants (trials providing individual participant data)

Trial	Focal seizures: n (%)		Male participants: n (%)[a]		Age at entry (years): Mean (SD), range[b]		Epilepsy duration (years): mean (SD), range[c]		Number of seizures in prior 6 months, median (range)[d]	
	PB	PHT	PB	PHT	PB	PHT	PB	PHT	PB	PHT
de Silva 1996[e]	5 (50%)	30 (56%)	4 (40%)	34 (63%)	9.1 (3.9) (4 to 15)	9.5 (3.4) (3 to 16)	1.3 (1.8) (0 to 5)	1.0 (2.1) (0 to 14)	3 (1 to 170)	3 (1 to 404)
Heller 1995	25 (43%)	28 (44%)	25 (43%)	34 (54%)	34.5 (15.1) (26 to 77)	33.5 (14.3) (14 to 72)	3.4 (6.6) (0 to 36)	3.8 (5.4) (0 to 24)	3 (1 to 579)	2 (1 to 575)
Mattson 1985	155 (100%)	165 (100%)	135 (88%)	145 (88%)	40.1 (15.3) (18 to 75)	40.8 (15.3) (18 to 81)	5.7 (7.9) (0.5 to 36)	6.6 (9.1) (0.5 to 59)	1 (1 to 14)	1 (1 to 26)
Ogunrin 2005	2 (11%)	3 (17%)	11 (61%)	11 (61%)	35.4 (6.2) (26 to 55)	18.8 (2.6) (15 to 26)	NA	NA	12 (6 to 42)	12 (6 to 18)
Pal 1998	26 (55%)	34 (72%)	23 (50%)	24 (52%)	11.5 (4.8) (2 to 18)	11.3 (5.2) (2 to 18)	3.8 (3.8) (0.5 to 17)	4.8 (4.3) 0.5 to 14	NA	NA

Footnotes

n: number of participants; NA: not available; PB: phenobarbitone; PHT:phenytoin SD: standard deviation

a. Sex was missing for four participants, two participants on PB from Mattson 1985 and two participants from Pal 1998 (one on PB and one on PHT). Proportions (%) are calculated based on non-missing data.

b. Age at randomisation was missing for two participants on PB from Mattson 1985

c. Epilepsy duration was missing for 41 participants; all 36 participants from Ogunrin 2005, two participants on PB from Mattson 1985, one participant on PB from Heller 1995 and two participants on PHT from Pal 1998

d. Number of seizures in the prior six months was missing for 97 participants, all 94 participants from Pal 1998 and three participants on PB from Mattson 1985

e. Randomised drug missing for 6 participants in de Silva 1996.

2 Outcomes considered and summary of results for trials with no IPD

Trial ¬	Number¬Randomised		Outcomes Reported ¬	Summary of Results¬ ¬
	PB	PHT		
Czapinski 1997	30	30	1. Proportion achieving 24-month remission at 3 years 2. Proportion "excluded" after randomisation due to adverse effects or no efficacy	1. PB: 60% PHT: 59% 2. PB: 33% PHT: 23%
Thilothammal 1996	51	52	1. Recurrence of Seizures 2. Side Effects	1. PB:16 out of 51 participants (31%) PHT: 14 out of 52 participants (27%) 2. PB:17 out of 51 participants (33%) PHT: 33 out of 52 participants (63%)

Footnotes

IPD: individual participant data, PB: phenobarbitone, PHT: phenytoin

3 Number of participants contributing to analysis - by epilepsy type

Trial	Epilepsy Type	Number randomised		Time to 6-month and 12-month remission[a]		Time to 1st seizure[a]		Time to treatment failure (any reason, adverse events or lack of efficacy)	
		PB	PHT	PB	PHT	PB	PHT	PB	PHT
de Silva 1996	Focal	5	30	5	30	5	30	5	30
	Generalised	5	24	5	24	5	24	5	23
	Total	10	54	10	54	10	54	10	53
Heller 1995	Focal	25	28	25	28	25	28	22	27
	Generalised	33	35	33	35	33	35	33	34
	Total	58	63	58	63	58	63	55	61
Mattson 1985	Focal	155	165	151	162	151	162	155	165
	Generalised	0	0	0	0	0	0	0	0
	Total	155	165	151	162	151	162	155	165
Ogunrin 2005	Focal	2	3	Information not available[b]		2	3	Information not available[b]	
	Generalised	16	15			16	15		
	Total	18	18			18	18		
Pal 1998	Focal	26	34	24	33	24	33	Information not available[b]	
	Generalised	21	13	20	13	20	13		
	Total	47	47	44	46	44	46		
TOTAL		288	347	263	325	281	343	220	279

Footnotes

PB: phenobarbitone, PHT: phenytoin

a. Seizure data after randomisation was not available for seven participants (four on PB and three on PHT) in Mattson 1985 and for four participants (three on PB and one on PHT) in Pal 1998. Therefore time to first seizure after randomisation and time to 6-month and 12-month remission could not be calculated for these outcomes.

b. For Pal 1998 information on time to treatment failure is not available. In Ogunrin 2005, all 36 participants completed the 12-week trial duration and no participants withdrew from the trial or from the allocated treatment, therefore only time to first seizure after randomisation could be calculated for this trial.

4 Reasons for premature discontinuation (treatment failure)

Reason for early termination	de Silva 1996[a]		Heller 1995[b]		Mattson 1985		Total		
	PB	PHT	PB	PHT	PB	PHT	PB	PHT	Total
Adverse events (event)	2	2	12	1	5	8	19	11	30
Lack of efficacy (event)	2	10	7	8	11	6	20	24	44
Both adverse events and lack of efficacy (event)	4	5	3	2	46	33	53	40	93
Non-compliance/protocol violation (event)	0	0	0	0	19	26	19	26	45
Illness or death (not treatment-related, censored)	0	0	0	0	13	11	13	11	24
Participant went into remission (censored)	1	24	3	14	0	0	4	38	42
Lost to follow-up (censored)	0	0	0	0	26	19	26	19	45
Other (censored)[c]	0	0	0	0	2	5	2	5	7
Completed the trial (censored)	1	12	30	38	33	57	64	107	171
Total	**10**	**53**	**55**	**63**	**155**	**165**	**220**	**281**	**501**

Footnotes

PB: phenobarbitone, PHT: phenytoin

a. One participant on PHT in de Silva 1996 has a missing treatment failure time and reason and did not contribute to analysis

b. Five participants from Heller 1995 (three on PB and two on PHT) had missing treatment failure time and did not contribute to analysis, but reasons for treatment failure were provided for the two participants on PHT.

c.Other reasons from Mattson 1985: participants developed other medical disorders including neurological and psychiatric disorders

5 Sensitivity analyses

Outcome[a]	Original analysis		de Silva 1996 (sensitivity analysis)[d]		Generalised onset and age at onset > 30 years classified as focal onset		Generalised onset and age at onset > 30 years classified as uncertain seizure type	
	Pooled HR (95% CI)	Test of subgroup differences	Pooled HR (95% CI)	Test of subgroup differences	Pooled HR (95% CI)	Test of subgroup differences	Pooled HR (95% CI)	Test of subgroup differences
Time to treatment failure (for any reason related to treatment)[b]	**F:** 1.46 (1.09 to 1.96), I^2 = 53% **G:** 4.04 (1.61 to 10.14), I^2 = 0% **O:** 1.61 (1.22 to 2.12), I^2 = 53%	Chi^2 = 4.25, df = 1, P = 0.04, I^2 = 76.5%	**F:** 1.36 (1.01 to 1.84), I^2 = 0% **G:** 4.22 (1.39 to 12.86), I^2 = 0% **O:** 1.47 (1.10 to 1.97), I^2 = 4%	Chi^2 = 3.68, df = 1, P = 0.06, I^2 = 72.8%	**F:** 1.54 (1.15 to 2.06), I^2 = 66% **G:** 3.18 (1.15 to 8.76), I^2 = 0% **O:** 1.63 (1.23 to 2.15), I^2 = 48%	Chi^2 = 1.81, df = 1, P = 0.18, I^2 = 44.7%	**F:** 1.46 (1.09 to 1.96), I^2 = 53% **G:** 3.18 (1.15 to 8.76), I^2 = 0% **U:** 9.08 (1.01 to 81.51), I^2 = NA **O:** 1.60 (1.21 to 2.11), I^2 = 44%	Chi^2 = 4.52, df = 2, P = 0.10, I^2 = 55.7%
Time to treatment failure due to adverse events[b]	**F:** 1.86 (1.27 to 2.73), I^2 = 73% **G:** 4.60 (1.17 to 17.98), I^2 = 0% **O:** 1.99 (1.37 to 2.87), I^2 = 58%	Chi^2 = 1.57, df = 1, P = 0.21, I^2 = 36.2%	**F:** 1.65 (1.11 to 2.46), I^2 = 27% **G:** 5.04 (1.04 to 24.53), I^2 = 0% **O:** 1.76 (1.20 to 2.59), I^2 = 21%	Chi^2 = 1.80, df = 1, P = 0.18, I^2 = 44.4%	**F:** 1.92 (1.31 to 2.81), I^2 = 79% **G:** 3.01 (0.75 to 12.07), I^2 = 0% **O:** 1.98 (1.37 to 2.86), I^2 = 59%	Chi^2 = 0.37, df = 1, P = 0.54, I^2 = 0%	Not available[e]	
Time to treatment failure due to lack of efficacy[b]	**F:** 1.73 (1.19 to 2.52), I^2 = 0% **G:** 3.40 (1.21 to 9.54), I^2 = 0% **O:** 1.87 (1.32 to 2.66), I^2 = 0%	Chi^2 = 1.45, df = 1, P = 0.23, I^2 = 31.1%	**F:** 1.66 (1.13 to 2.44), I^2 = 0% **G:** 3.22 (0.85 to 12.21), I^2 = 0% **O:** 1.75 (1.21 to 2.53), I^2 = 0%	Chi^2 = 0.88, df = 1, P = 0.35, I^2 = 0%	**F:** 1.76 (1.22 to 2.55), I^2 = 0% **G:** 3.44 (1.11 to 10.72), I^2 = 0% **O:** 1.88 (1.32 to 2.67), I^2 = 0%	Chi^2 = 1.21, df = 1, P = 0.27, I^2 = 17.4%	**F:** 1.73 (1.19 to 2.52), I^2 = 0% **G:** 3.44 (1.11 to 10.72), I^2 = 0% **U:** 2.46 (0.15 to 39.49), I^2 = NA **O:** 1.86 (1.31 to 2.64), I^2 = 0%	Chi^2 = 1.31, df = 2, P = 0.52, I^2 = 0%

Outcome[a]	Original analysis		de Silva 1996 (sensitivity analysis)[d]		Generalised onset and age at onset > 30 years classified as focal onset		Generalised onset and age at onset > 30 years classified as uncertain seizure type	
	Pooled HR (95% CI)	Test of subgroup differences	Pooled HR (95% CI)	Test of subgroup differences	Pooled HR (95% CI)	Test of subgroup differences	Pooled HR (95% CI)	Test of subgroup differences
Time to first seizure[c]	**F:** 0.81 (0.63 to 1.04), I^2 = 0% **G**: 1.06 (0.70 to 1.62), I^2 = 27% **O:** 0.87 (0.70 to 1.08), I^2 = 0%	Chi^2 = 1.17, df = 1, P = 0.28, I^2 = 14.4%	**F:** 0.83 (0.64 to 1.08), I^2 = 0% **G:** 1.00 (0.65 to 1.55), I^2 = 5% **O:** 0.87 (0.70 to 1.09), I^2 = 0%	Chi^2 = 0.50, df = 1 (P = 0.48), I^2 = 0%	**F:** 0.83 (0.65 to 1.06), I^2 = 0% **G:** 1.08 (0.65 to 1.79), I^2 = 0% **O:** 0.87 (0.70 to 1.09), I^2 = 0%	Chi^2 = 0.81, df = 1, P = 0.37, I^2 = 0%	**F:** 0.81 (0.63 to 1.04), I^2 = 0% **G:** 1.08 (0.65 to 1.79), I^2 = 0% **U**: 1.04 (0.43 to 2.50), I^2 = 0% **O**: 0.87 (0.69 to 1.08), I^2 = 0%	Chi^2 = 1.15, df = 2, P = 0.56, I^2 = 0%
Time to 12-month remission[b]	**F:** 0.96 (0.70 to 1.33), I^2 = 9% **G:** 0.77 (0.46 to 1.28), I^2 = 0% **O:** 0.90 (0.69 to 1.19), I^2 = 0%	Chi^2 = 0.53, df = 1, P = 0.47, I^2 = 0%	**F:** 0.89 (0.63 to 1.24), I^2 = 3% **G:** 0.78 (0.46 to 1.31), I^2 = 0% **O:** 0.85 (0.64 to 1.13), I^2 = 0%	Chi^2 = 0.18, df = 1 (P = 0.67), I^2 = 0%	**F:** 0.97 (0.72 to 1.31), I^2 = 8% **G:** 0.54 (0.28 to 1.07), I^2 = 0% **O:** 0.88 (0.67 to 1.16), I^2 = 0%	Chi^2 = 2.37, df = 1, P = 0.12, I^2 = 57.9%	**F:** 0.96 (0.70 to 1.33), I^2 = 9% **G:** 0.54 (0.28 to 1.07), I^2 = 0% **U**: 1.00 (0.43 to 2.32), I^2 = NA **O**: 0.88 (0.67 to 1.16), I^2 = 0%	Chi^2 = 2.36, df = 2, P = 0.31, I^2 = 15.2%
Time to 6-month remission[b]	**F**: 0.94 (0.71 to 1.25), I^2 = 0% **G:** 0.82 (0.52 to 1.29), I^2 = 30% **O:** 0.91 (0.71 to 1.15), I^2 = 0%	Chi^2 = 0.27, df = 1, P = 0.60, I^2 = 0%	**F:** 0.89 (0.67 to 1.19), I^2 = 0% **G:** 0.84 (0.53 to 1.34), I^2 = 22% **O:** 0.88 (0.69 to 1.12), I^2 = 0%	Chi^2 = 0.05, df = 1 (P = 0.82), I^2 = 0%	**F** 0.93 (0.72 to 1.21):, I^2 = 0% **G:** 0.65 (0.35 to 1.20), I^2 = 45% **O:** 0.88 (0.69 to 1.12), I^2 = 16%	Chi^2 = 1.10, df = 1, P = 0.29, I^2 = 8.9%	**F:** 0.94 (0.71 to 1.25), I^2 = 0% **G:** 0.65 (0.35 to 1.20), I^2 = 45% **U**: 0.87 (0.40 to 1.88), I^2 = NA **O**: 0.88 (0.69 to 1.13), I^2 = 2%	Chi^2 = 1.16, df = 2, P = 0.56, I^2 = 0%

Footnotes

Chi^2: Chi^2 statistic; df: degrees of freedom of Chi^2 distribution; F: focal epilepsy; G: generalised epilepsy; NA: not applicable; O: overall (all participants); P: P value (< 0.05 are classified as statistically significant); U: uncertain epilepsy.

a. For time to treatment failure and time to first seizure, HR < 1 indicates a clinical advantage for carbamazepine and for time to 12-month and six-month remission, HR < 1 indicates a clinical advantage for phenobarbitone. All results presented are calculated from fixed-effect meta-analysis.

b. 33 participants reclassified to focal epilepsy or uncertain epilepsy type from Heller 1995. Heterogeneity (I^2) is not applicable for the uncertain epilepsy type group as only one study (Heller 1995) contributes to this estimate.

c. 46 participants reclassified to focal epilepsy or uncertain epilepsy type from Heller 1995 and Ogunrin 2005.

d. Sensitivity analysis including only the participants in de Silva 1996, who were randomised before the phenobarbitone arm was withdrawn.

e. This sensitivity analysis could not be conducted as no individuals with uncertain seizure type withdrew from phenytoin in Heller 1995

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Classification pending references

Data and analyses

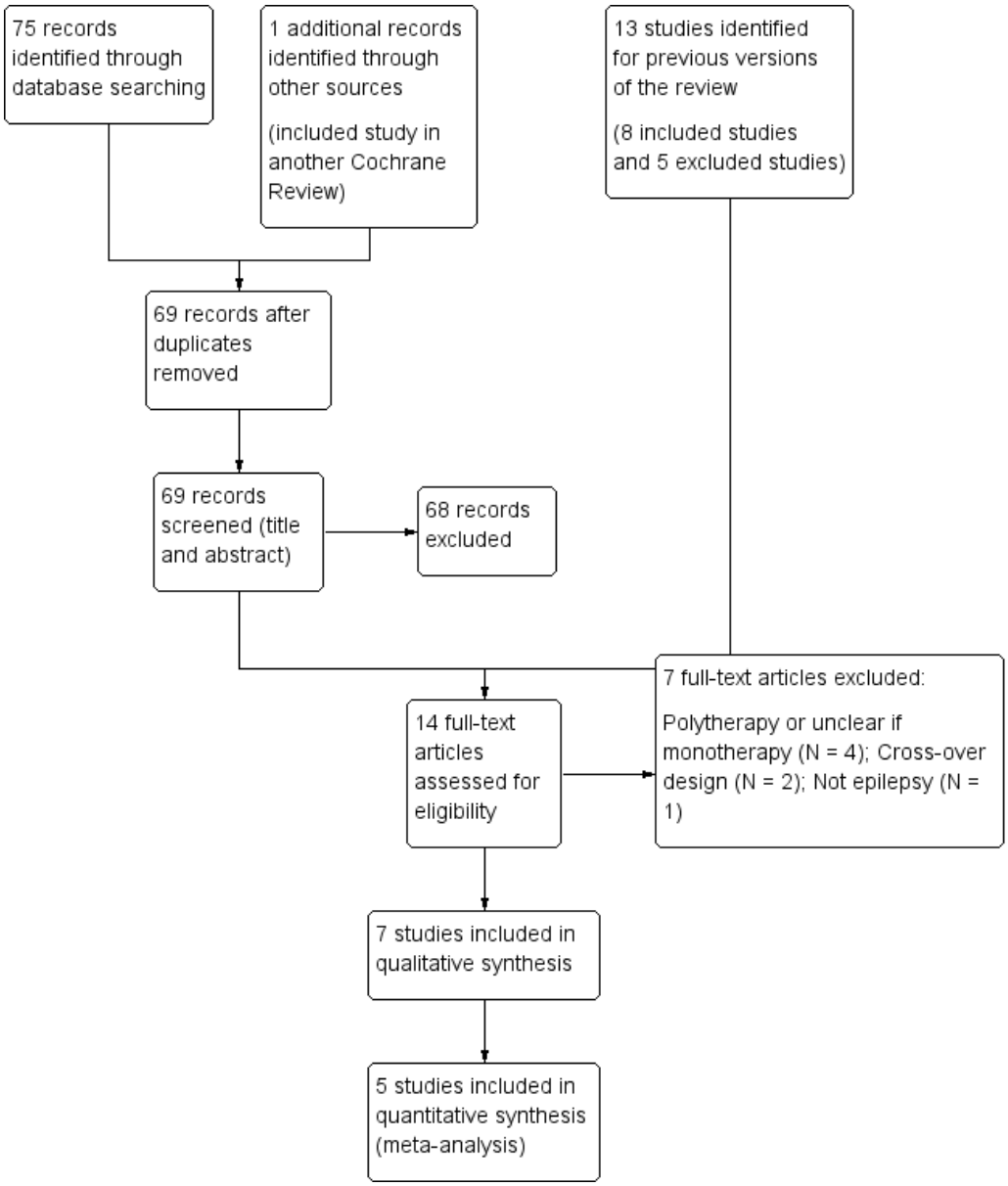
1 Phenobarbitone (PB) versus phenytoin (PHT) monotherapy

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
1.1 Time to treatment failure (any reason related to the treatment)	3	499	Hazard Ratio(IV, Fixed, 95% CI)	1.61 [1.22, 2.12]
1.2 Time to treatment failure due to adverse events	3	499	Hazard Ratio(IV, Fixed, 95% CI)	2.01 [1.39, 2.90]
1.3 Time to treatment failure due to lack of efficacy	3	499	Hazard Ratio(IV, Fixed, 95% CI)	1.85 [1.31, 2.62]
1.4 Time to treatment failure (any reason related to the treatment) - by epilepsy type	3	499	Hazard Ratio(IV, Fixed, 95% CI)	1.61 [1.22, 2.12]
1.4.1 Focal onset seizures	3	404	Hazard Ratio(IV, Fixed, 95% CI)	1.46 [1.09, 1.96]
1.4.2 Generalised onset seizures	2	95	Hazard Ratio(IV, Fixed, 95% CI)	4.04 [1.61, 10.14]
1.5 Time to treatment failure due to adverse events - by epilepsy type	3	499	Hazard Ratio(IV, Fixed, 95% CI)	1.99 [1.37, 2.87]
1.5.1 Focal onset seizures	3	404	Hazard Ratio(IV, Fixed, 95% CI)	1.86 [1.27, 2.73]
1.5.2 Generalised onset seizures	2	95	Hazard Ratio(IV, Fixed, 95% CI)	4.60 [1.17, 17.98]
1.6 Time to treatment failure due to lack of efficacy - by epilepsy type	3	499	Hazard Ratio(IV, Fixed, 95% CI)	1.87 [1.32, 2.66]
1.6.1 Focal onset seizures	3	404	Hazard Ratio(IV, Fixed, 95% CI)	1.73 [1.19, 2.52]
1.6.2 Generalised onset seizures	2	95	Hazard Ratio(IV, Fixed, 95% CI)	3.40 [1.21, 9.54]

1.7 Time to treatment failure (any reason related to the treatment) - by age of participants	3	499	Hazard Ratio(IV, Fixed, 95% CI)	1.61 [1.22, 2.12]
1.7.1 Adults only	2	436	Hazard Ratio(IV, Fixed, 95% CI)	1.46 [1.09, 1.95]
1.7.2 Children only	1	63	Hazard Ratio(IV, Fixed, 95% CI)	3.93 [1.65, 9.34]
1.8 Time to treatment failure due to adverse events - by age of participants	3	499	Hazard Ratio(IV, Fixed, 95% CI)	2.01 [1.39, 2.90]
1.8.1 Adults only	2	436	Hazard Ratio(IV, Fixed, 95% CI)	1.75 [1.18, 2.58]
1.8.2 Children only	1	63	Hazard Ratio(IV, Fixed, 95% CI)	5.99 [1.99, 17.96]
1.9 Time to treatment failure (any reason related to the treatment) - by blinded study design	3	499	Hazard Ratio(IV, Fixed, 95% CI)	1.61 [1.22, 2.12]
1.9.1 Open-label design	2	179	Hazard Ratio(IV, Fixed, 95% CI)	2.92 [1.69, 5.03]
1.9.2 Double-blind design	1	320	Hazard Ratio(IV, Fixed, 95% CI)	1.31 [0.95, 1.81]
1.10 Time to treatment failure due to adverse events - by blinded study design	3	499	Hazard Ratio(IV, Fixed, 95% CI)	2.01 [1.39, 2.90]
1.10.1 Open-label design	2	179	Hazard Ratio(IV, Fixed, 95% CI)	6.25 [2.75, 14.22]
1.10.2 Double-blind design	1	320	Hazard Ratio(IV, Fixed, 95% CI)	1.51 [1.00, 2.28]
1.11 Time to first seizure after randomisation	5	624	Hazard Ratio(IV, Fixed, 95% CI)	0.85 [0.69, 1.06]
1.12 Time to first seizure after randomisation - by epilepsy type	5	624	Hazard Ratio(IV, Fixed, 95% CI)	0.87 [0.70, 1.08]
1.12.1 Focal onset seizures	5	463	Hazard Ratio(IV, Fixed, 95% CI)	0.81 [0.63, 1.04]
1.12.2 Generalised onset seizures	4	161	Hazard Ratio(IV, Fixed, 95% CI)	1.06 [0.70, 1.62]
1.13 Time to achieve 12-month remission from seizures	4	588	Hazard Ratio(IV, Fixed, 95% CI)	0.90 [0.69, 1.18]
1.14 Time to achieve 12 month remission - by seizure type	4	588	Hazard Ratio(IV, Fixed, 95% CI)	0.90 [0.69, 1.19]
1.14.1 Focal onset seizures	4	458	Hazard Ratio(IV, Fixed, 95% CI)	0.96 [0.70, 1.33]
1.14.2 Generalised onset seizures	3	130	Hazard Ratio(IV, Fixed, 95% CI)	0.77 [0.46, 1.28]
1.15 Time to achieve 6-month remission	4	588	Hazard Ratio(IV, Fixed, 95% CI)	0.93 [0.73, 1.18]
1.16 Time to achieve 6-month remission - by seizure type	4	588	Hazard Ratio(IV, Fixed, 95% CI)	0.91 [0.71, 1.15]
1.16.1 Focal onset seizures	4	458	Hazard Ratio(IV, Fixed, 95% CI)	0.94 [0.71, 1.25]
1.16.2 Generalised onset seizures	3	130	Hazard Ratio(IV, Fixed, 95% CI)	0.82 [0.52, 1.29]
1.17 Time to achieve 6-month remission - interval censored	4		Hazard Ratio(IV, Fixed, 95% CI)	Subtotals only
1.17.1 remission before 300 days	4	588	Hazard Ratio(IV, Fixed, 95% CI)	1.03 [0.79, 1.34]
1.17.2 remission at 300 days or later	3	113	Hazard Ratio(IV, Fixed, 95% CI)	0.78 [0.60, 1.00]

Figures

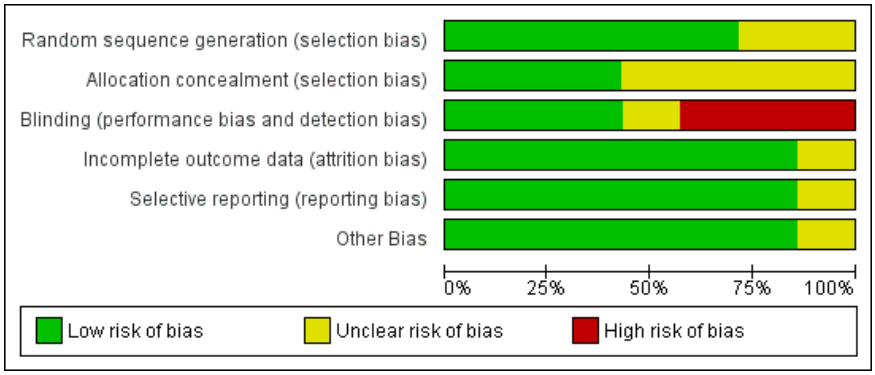
Figure 1



Caption

Study flow diagram.

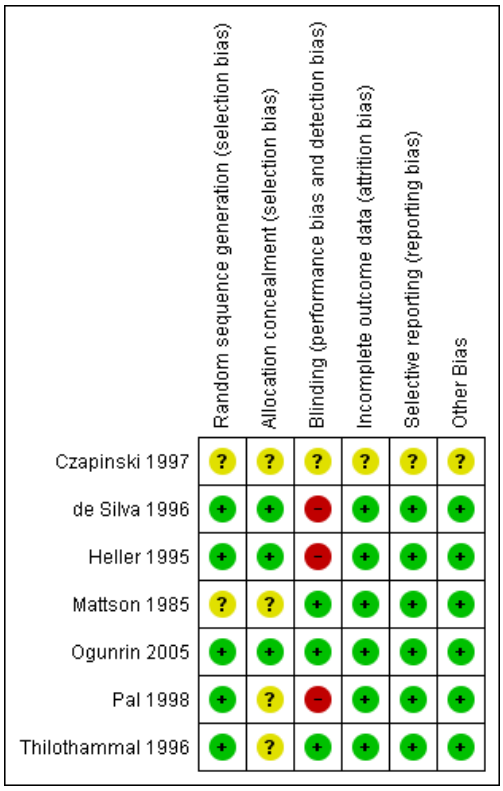
Figure 2



Caption

'Risk of bias' graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

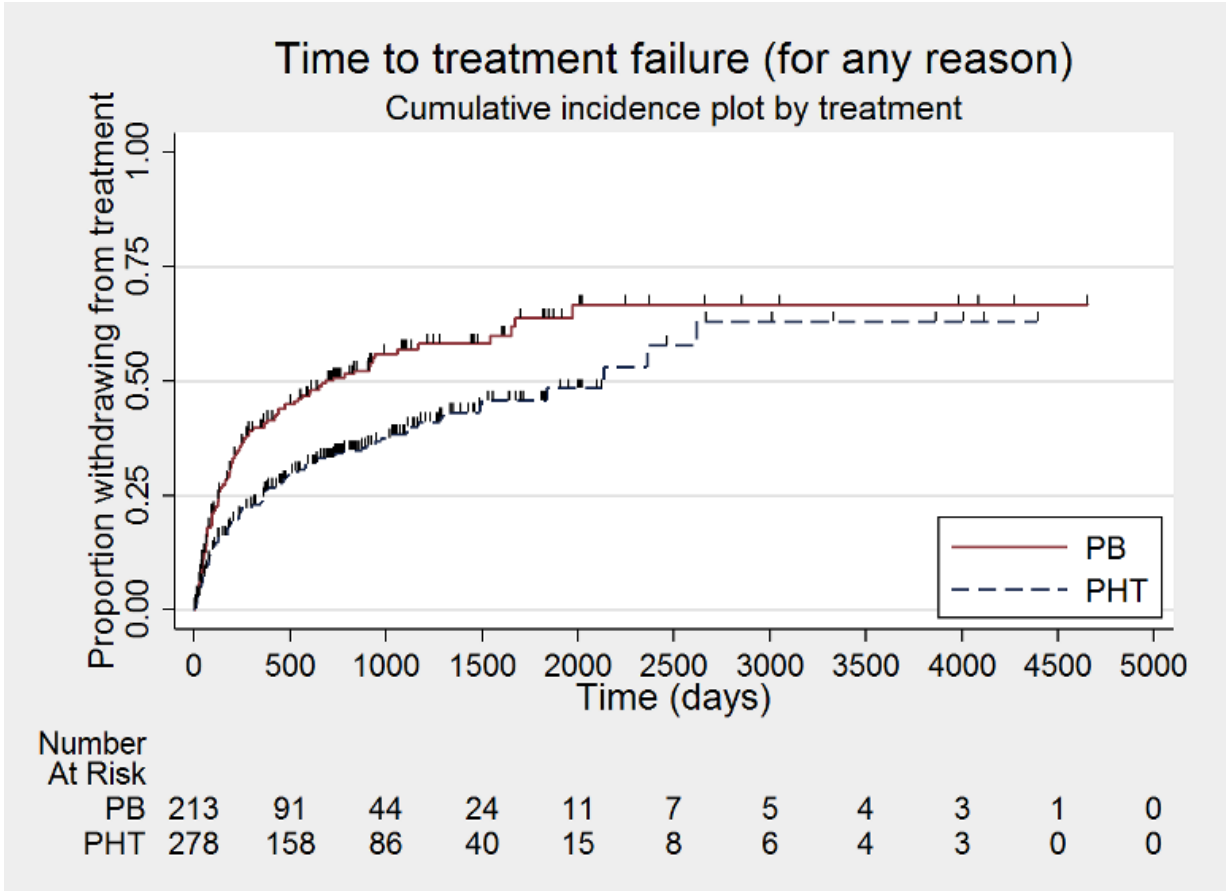
Figure 3



Caption

'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.

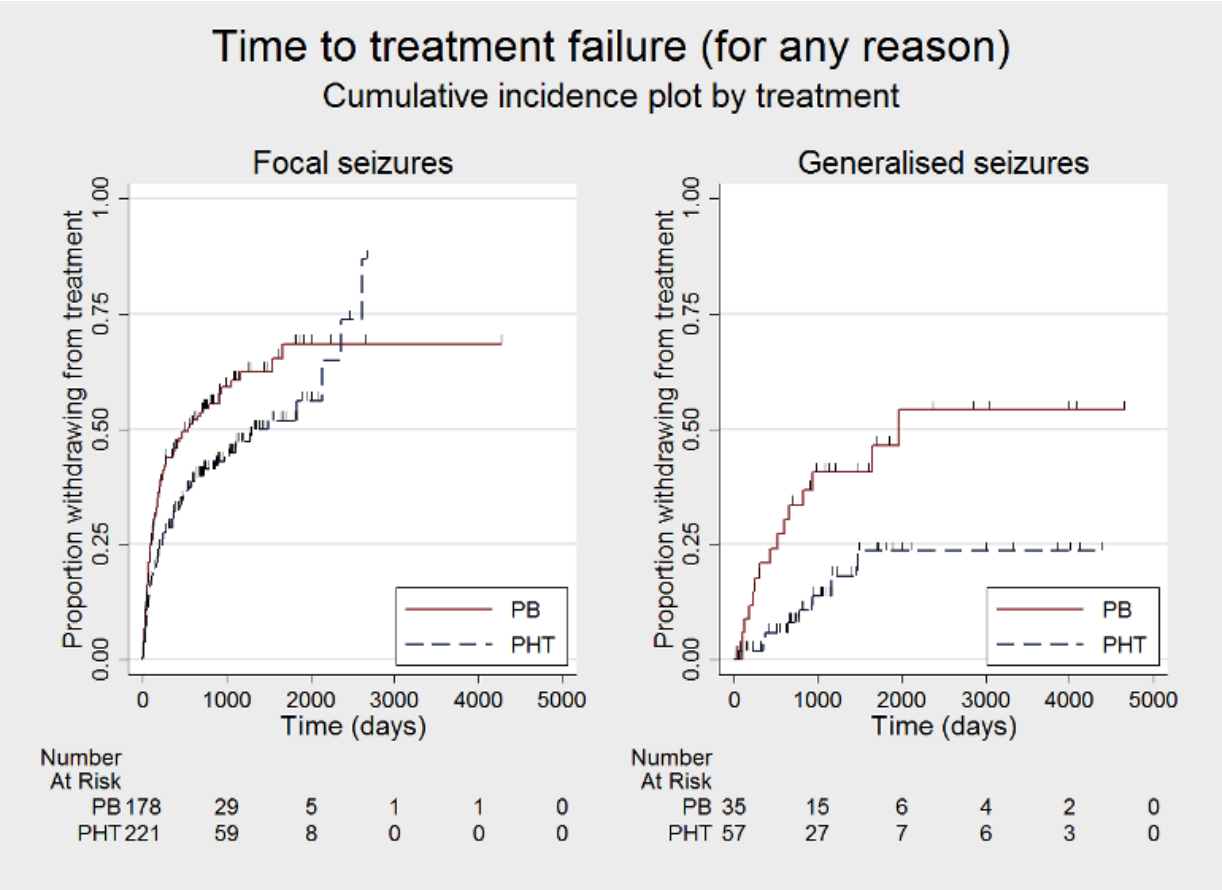
Figure 4



Caption

Time to treatment failure - any reason related to the treatment (PB: phenobarbitone; PHT: phenytoin)

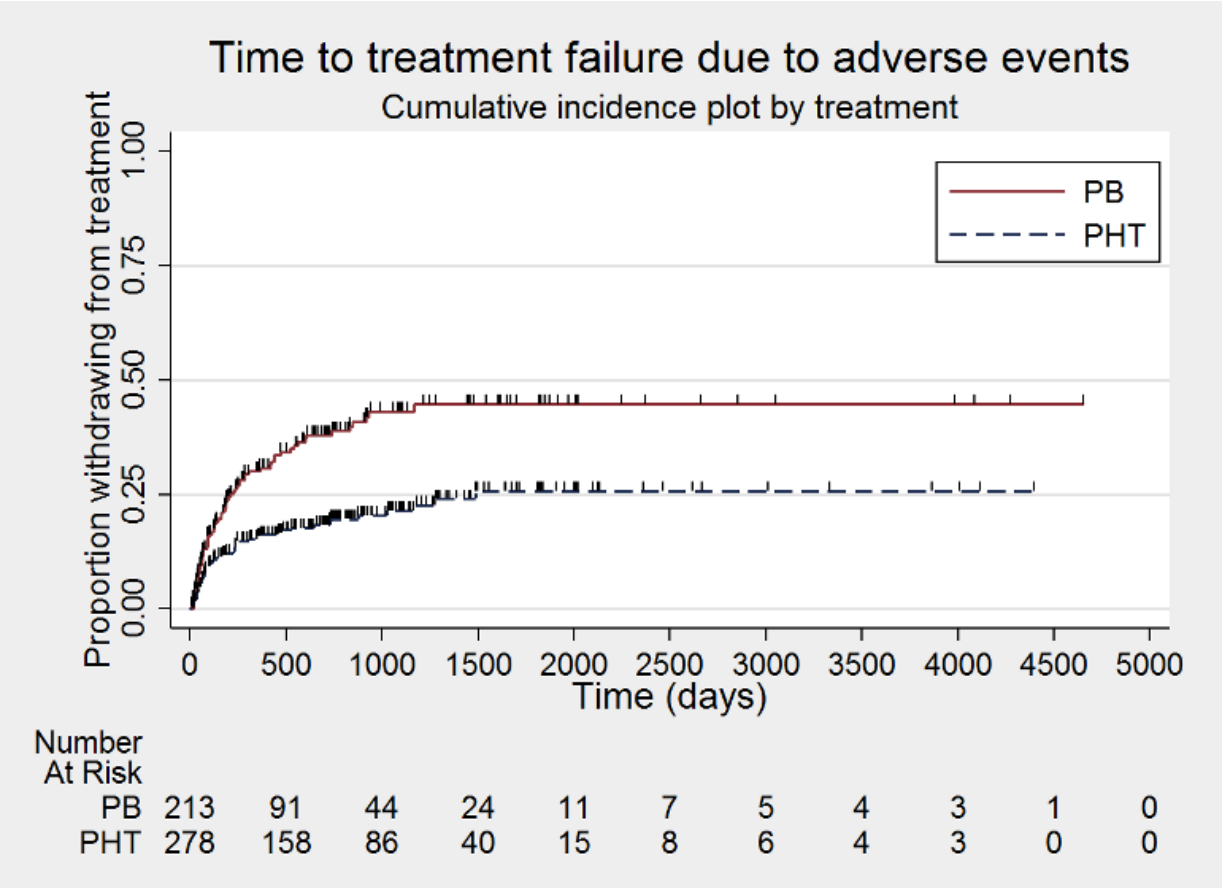
Figure 5



Caption

Time to treatment failure – any reason related to the treatment, by epilepsy type (PB: phenobarbitone; PHT: phenytoin)

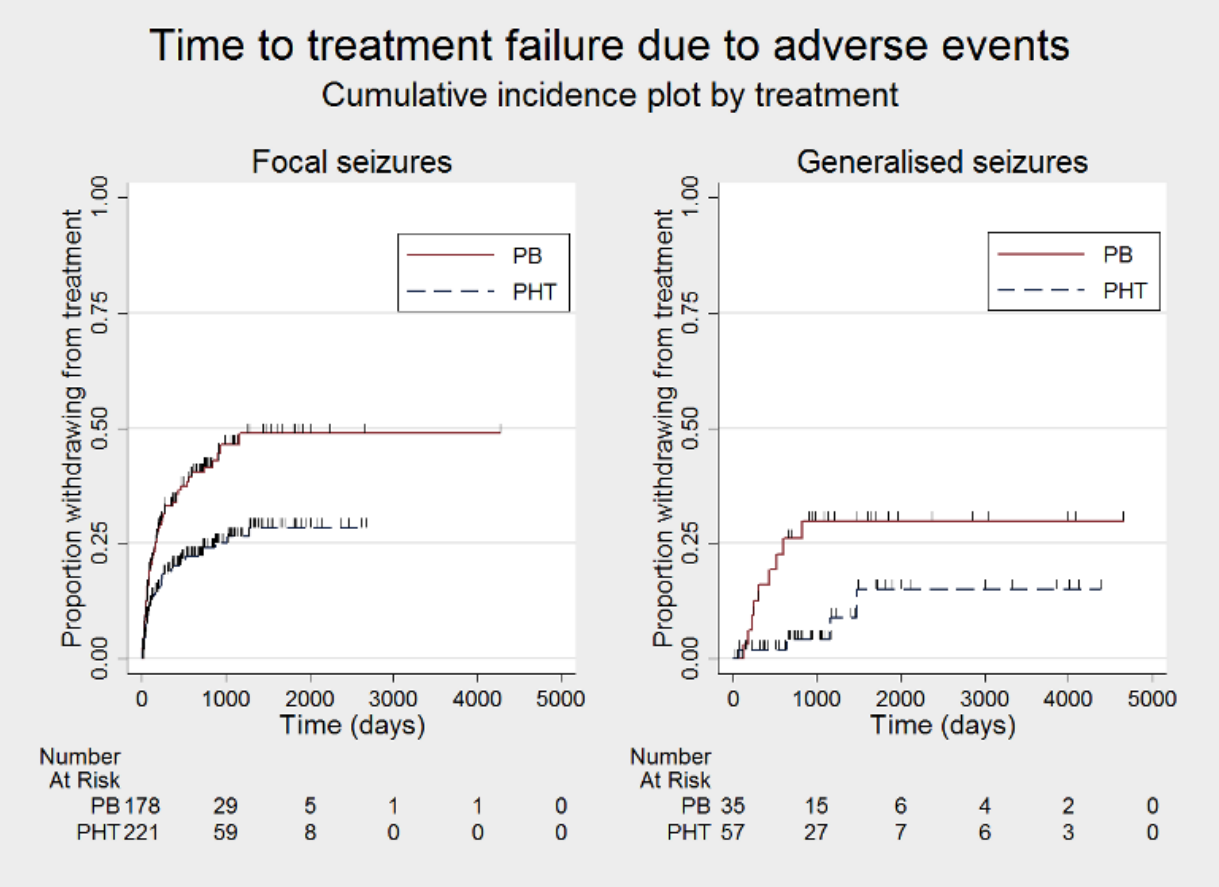
Figure 6



Caption

Time to treatment failure due to adverse events (PB: phenobarbitone; PHT: phenytoin)

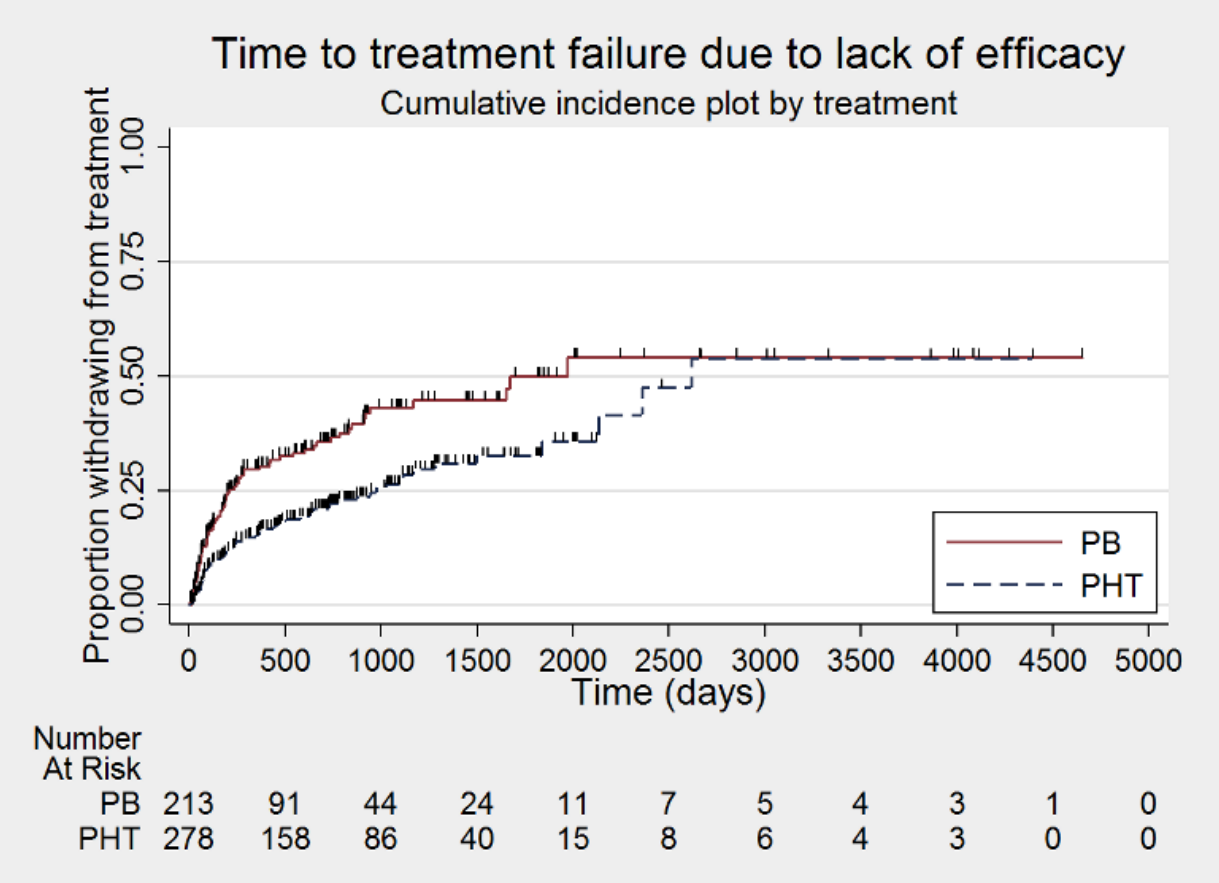
Figure 7



Caption

Time to treatment failure due to adverse events, by epilepsy type (PB: phenobarbitone; PHT: phenytoin)

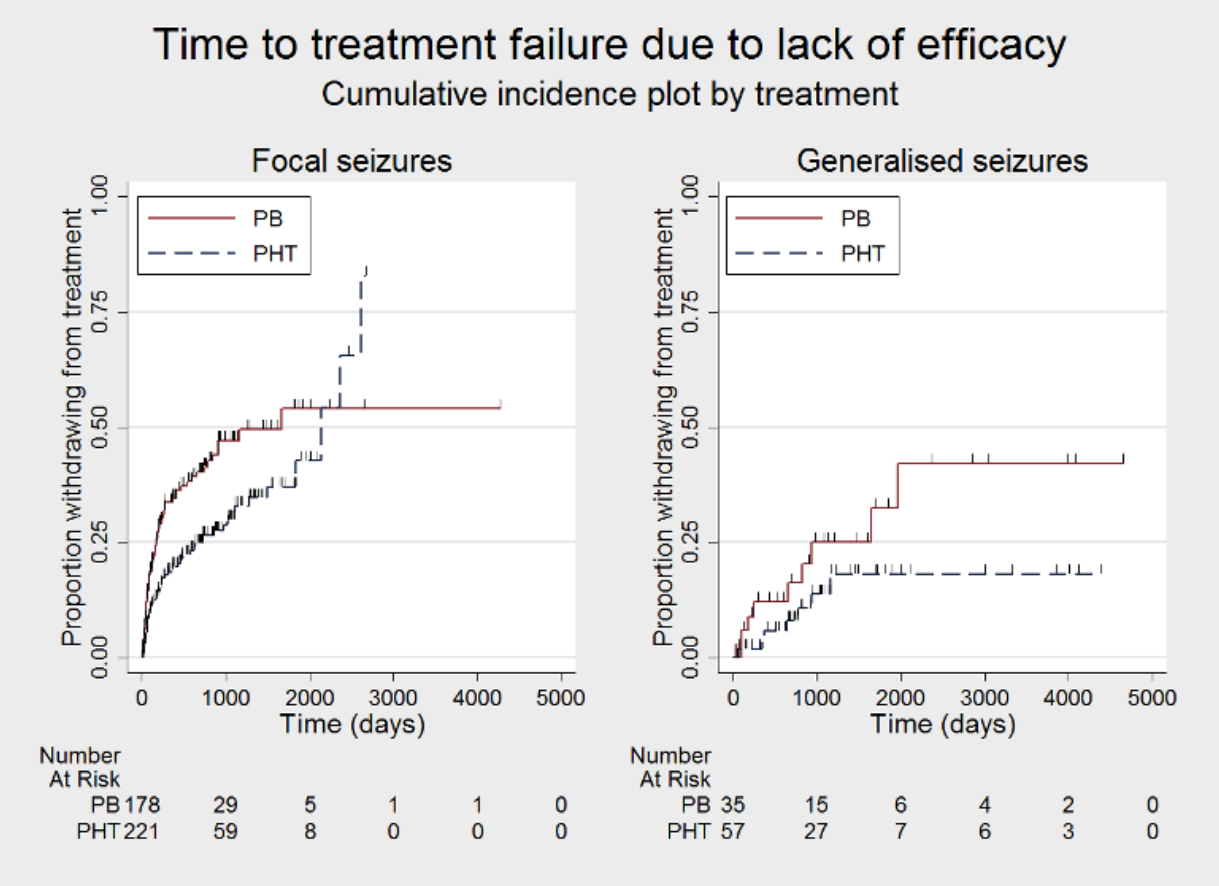
Figure 8



Caption

Time to treatment failure due to lack of efficacy (PB: phenobarbitone; PHT: phenytoin)

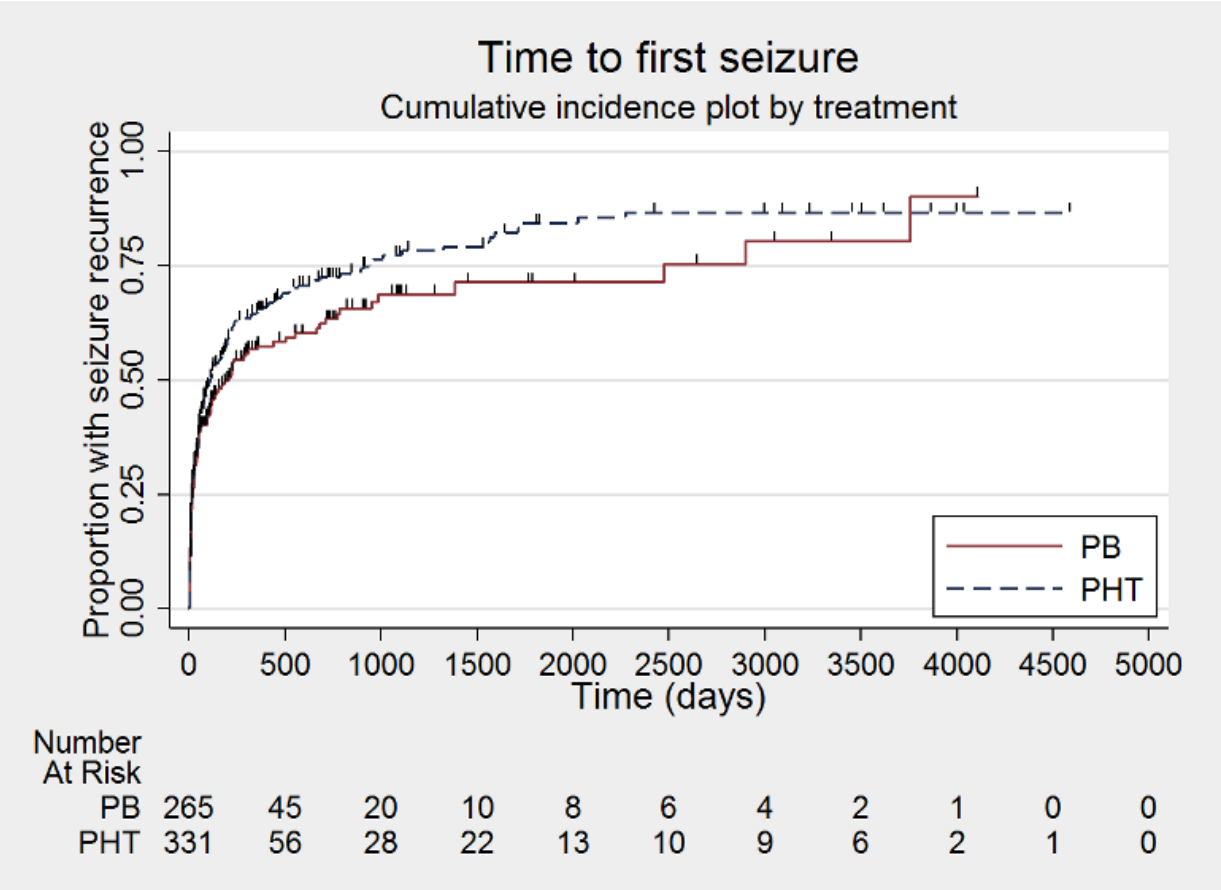
Figure 9



Caption

Time to treatment failure due to lack of efficacy, by epilepsy type (PB: phenobarbitone; PHT: phenytoin)

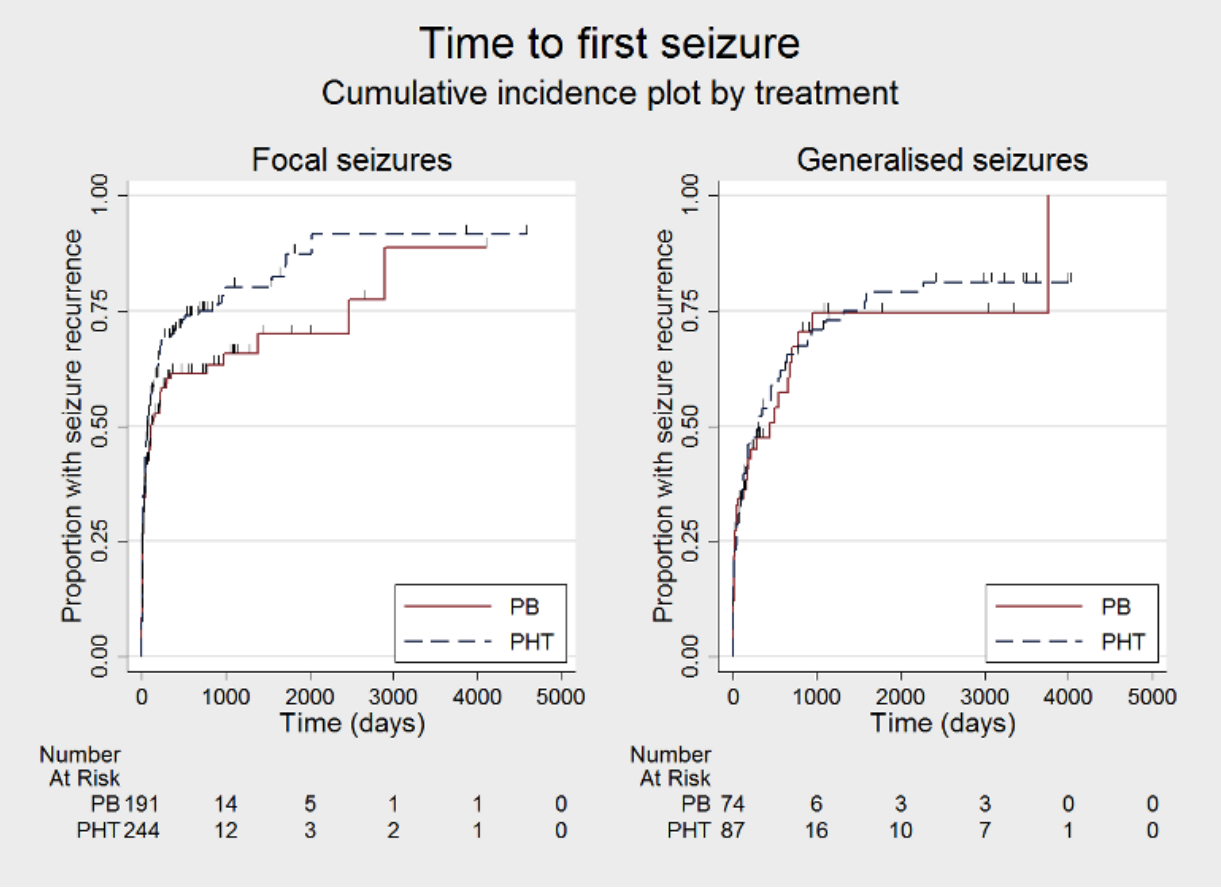
Figure 10



Caption

Time to first seizure (PB: phenobarbitone; PHT: phenytoin)

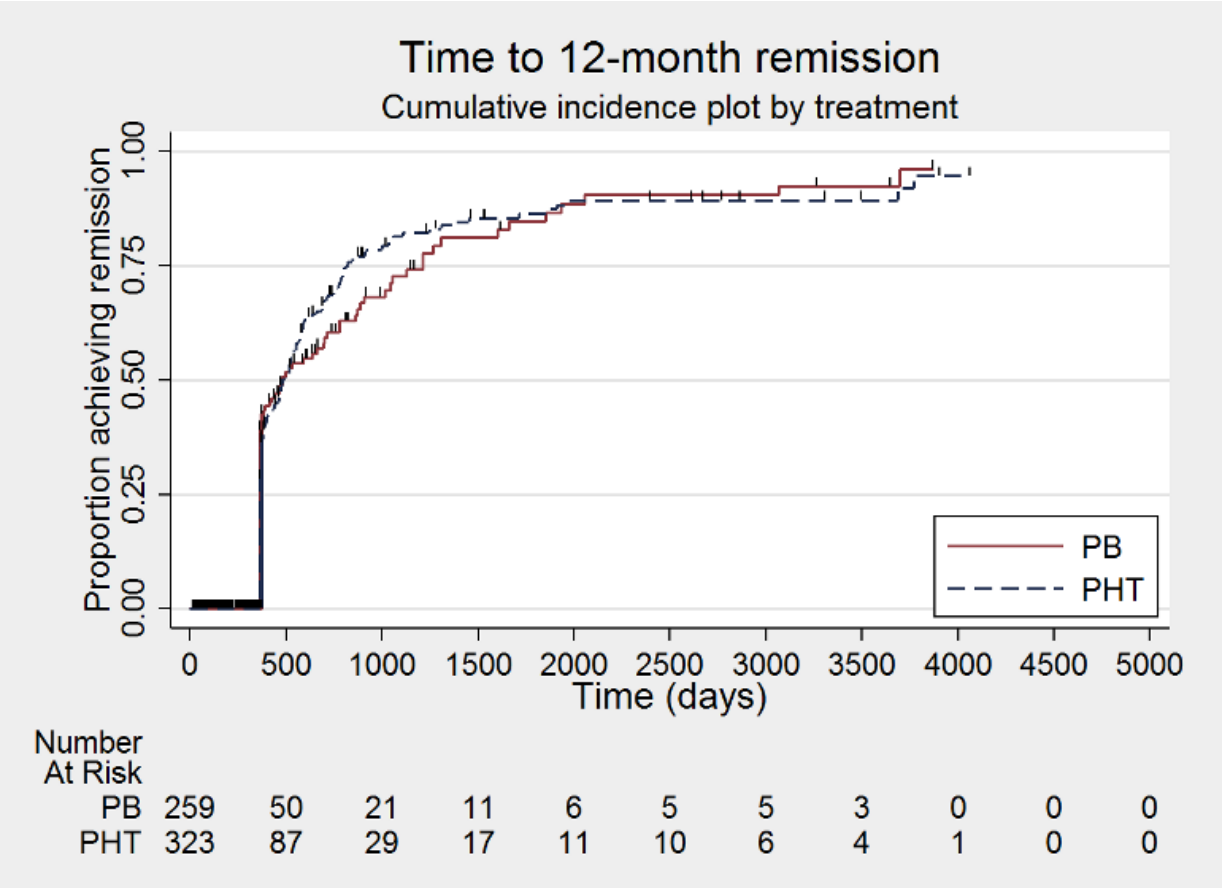
Figure 11



Caption

Time to first seizure, by epilepsy type (PB: phenobarbitone; PHT: phenytoin)

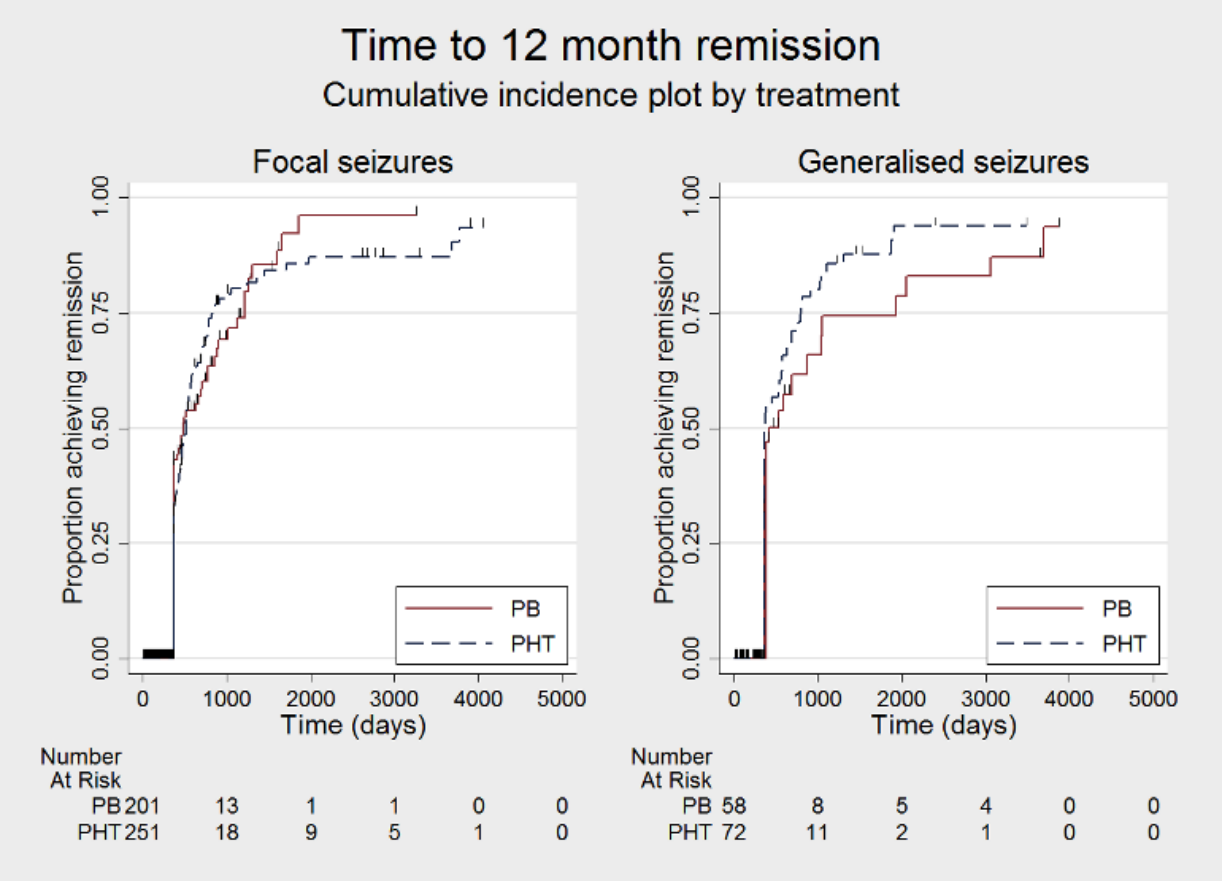
Figure 12



Caption

Time to 12 month remission (PB: phenobarbitone; PHT: phenytoin)

Figure 13

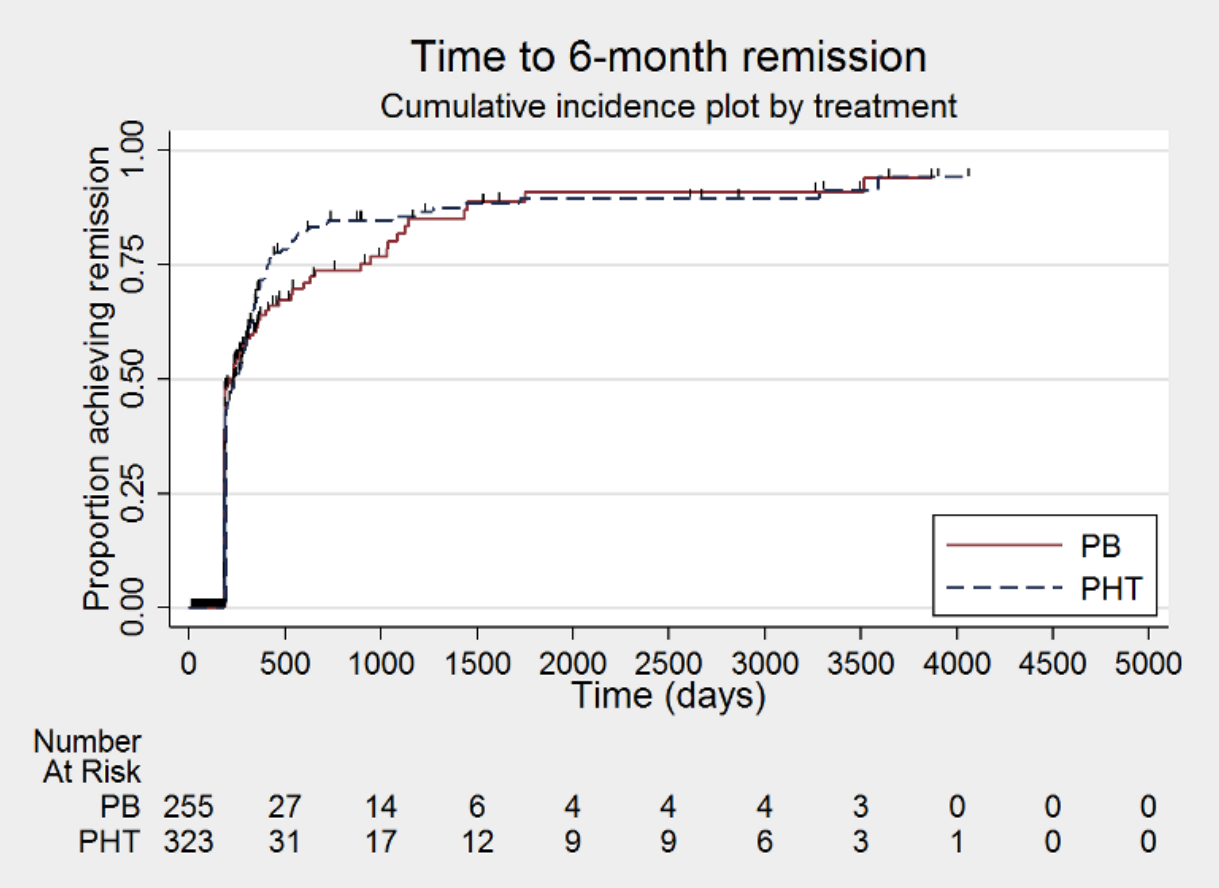


Caption

Caption

Time to 12 month remission, by epilepsy type (PB: phenobarbitone; PHT: phenytoin)

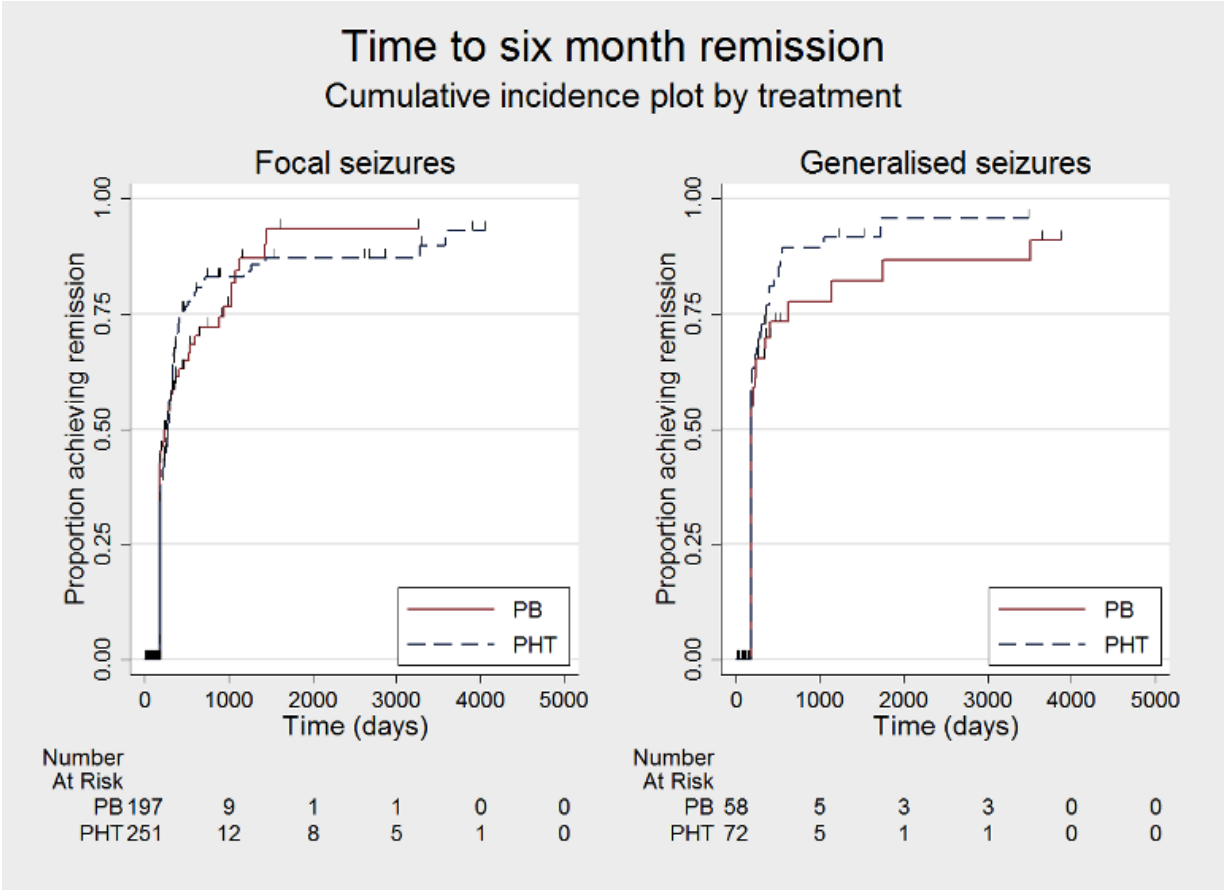
Figure 14



Caption

Time to 6 month remission (PB: phenobarbitone; PHT: phenytoin)

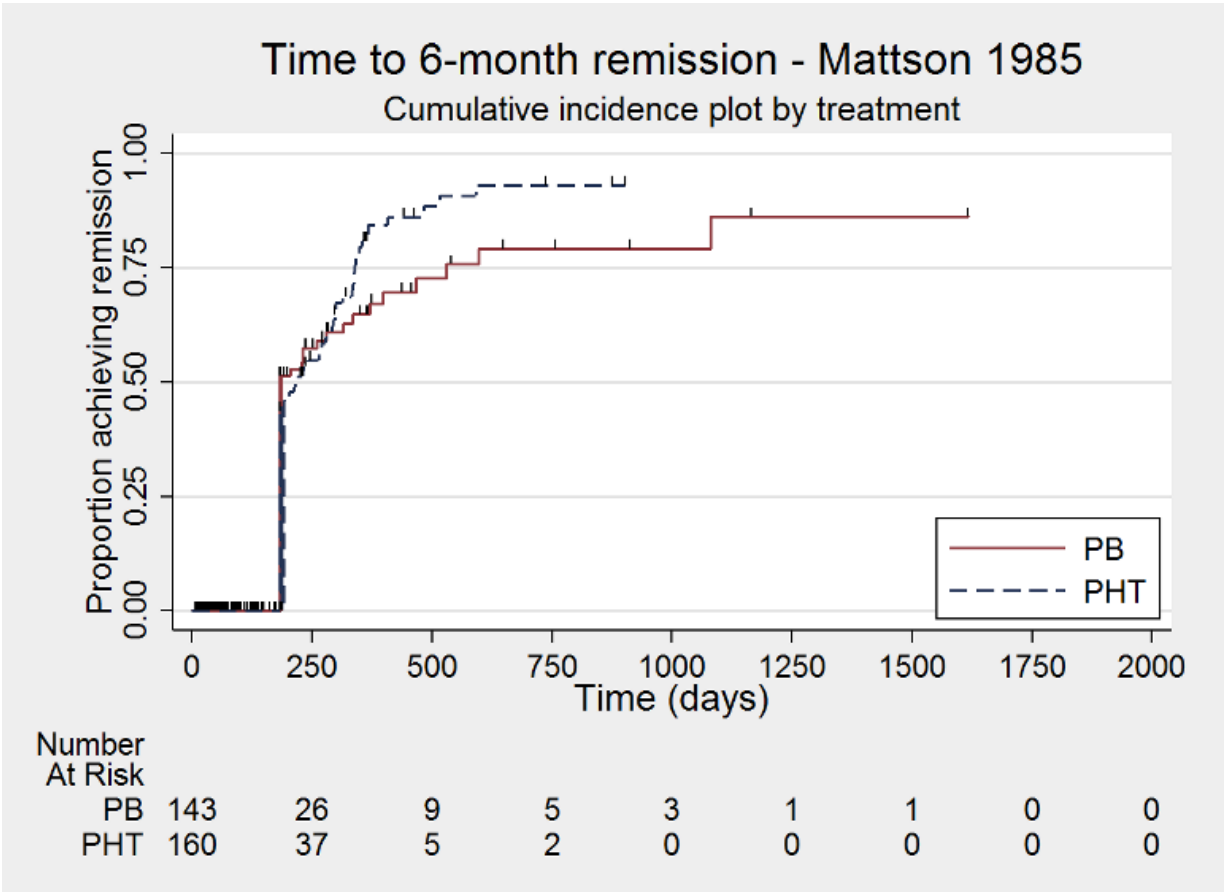
Figure 15



Caption

Time to 6 month remission, by epilepsy type (PB: phenobarbitone; PHT: phenytoin)

Figure 16



Caption

Time to 6 month remission – Mattson 1985 (Proportional Hazards Check)

Sources of support

Internal sources

- University of Liverpool, UK
- Royal Liverpool and Broadgreen Hospital Trust, UK

External sources

- Medical Research Council, UK
- National Institute of Health Research (NIHR), UK

Feedback

Appendices

1 CRS Web search strategy

1. MeSH DESCRIPTOR Phenobarbital Explode All AND CENTRAL:TARGET

2. (Fenobarbit* or Luminal or Phenobarbit* or Phenylethylbarbit* or Phenylethylmalonylurea or Prominal):AB,KW,MC,MH,TI AND CENTRAL:TARGET

3. #1 OR #2 AND CENTRAL:TARGET

4. MeSH DESCRIPTOR Phenytoin Explode All AND CENTRAL:TARGET

5. (Difenilhidantoin* or Dihydantoin or Dilantin or Diphenylan or Diphenylhydantoin* or Diphenylhydatanoin* or Dwufenylohydantoin* or Epanutin or Eptoin or Fenitoin* or Fenytoin* or Phenytek or Phenytoin*):AB,KW,MC,MH,TI AND CENTRAL:TARGET

6. #4 OR #5 AND CENTRAL:TARGET

7. #3 AND #6 AND CENTRAL:TARGET

8. MESH DESCRIPTOR Epilepsy EXPLODE ALL AND CENTRAL:TARGET

9. MESH DESCRIPTOR Seizures EXPLODE ALL AND CENTRAL:TARGET

10. (epilep* OR seizure* OR convuls*):AB,KW,MC,MH,TI AND CENTRAL:TARGET

11. #8 OR #9 OR #10 AND CENTRAL:TARGET

12. #7 AND #11

13. ((adjunct* or "add-on" or "add on" or adjuvant* or combination* or polytherap*) not (monotherap* or alone or singl*)):TI AND CENTRAL:TARGET

14. #12 NOT #13

15. #14 AND >30/07/2014:CRSCREATED

2 MEDLINE search strategy

The following is based on the Cochrane Highly Sensitive Search Strategy for identifying randomised trials in MEDLINE (Lefebvre 2011).

1. exp Phenobarbital/

2. (Fenobarbit$ or Luminal or Phenobarbit$ or Phenylethylbarbit$ or Phenylethylmalonylurea or Prominal).tw.

3. 1 or 2

4. exp Phenytoin/

5. (Difenilhidantoin$ or Dihydantoin or Dilantin or Diphenylan or Diphenylhydantoin$ or Diphenylhydatanoin$ or Dwufenylohydantoin$ or Epanutin or Eptoin or Fenitoin$ or Fenytoin$ or Phenytek or Phenytoin$).tw.

6. 4 or 5

7. 3 and 6

8. exp Epilepsy/

9. exp Seizures/

10. (epilep$ or seizure$ or convuls$).tw.

11. 8 or 9 or 10

12. exp *Pre-Eclampsia/ or exp *Eclampsia/

13. 11 not 12

14. (randomized controlled trial or controlled clinical trial or pragmatic clinical trial).pt. or (randomi?ed or placebo or randomly).ab.

15. clinical trials as topic.sh.

16. trial.ti.

17. 14 or 15 or 16

18. exp animals/ not humans.sh.

19. 17 not 18

20. 7 and 13 and 19

21. ((adjunct$ or "add-on" or "add on" or adjuvant$ or combination$ or polytherap$) not (monotherap$ or alone or singl$)).ti.

22. 20 not 21

23. limit 22 to ed=20140730-20180821

24. 22 not (1$ or 2$).ed.

25. 24 and (2014$ or 2015$ or 2016$ or 2017$ or 2018$).dt.

26. 23 or 25

3 ClinicalTrials.gov search strategy

Interventional Studies | Epilepsy | Phenobarbitone AND phenytoin

4 ICTRP search strategy

Condition: epilepsy

Intervention: phenobarbitone AND phenytoin

Recruitment status: all

Phases: 2, 3, 4